Exhibit 6

EXPERT REPORT OF

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I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist, and co-founder of BioPolicy Solutions LLC. BioPolicy Solutions has offices in Houston, TX and Ventura, CA, and is a consulting firm that works at the interface of biological science, regulatory affairs, and business decisions to provide its clients with science-based solutions to issues associated with development and marketing of existing products as well as new technologies. Before BioPolicy Solutions was formed in 2020, I was principal in the consulting firm known as Integrative Biostrategies (2001 to 2020) and head of a consulting firm known as Plunkett & Associates (1997 to 2001).

2. I am board-certified as a Diplomate of the American Board of Toxicology and am a registered patent agent in the US (USPTO Registration No. 45.015). I am a member of several professional organizations and have authored or co-authored numerous scientific publications, including a book chapter on pharmacovigilance practices in the United States and another on the regulation of food additives (listed in Appendix A). I have over thirty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels. I currently hold an adjunct appointment in the Department of Environmental Science, Baylor University (2017 to present).

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides.

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neuroscience laboratory of the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

5. From September 1986 to June 1989, I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where I performed research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology, as well as neuroscience. During this time, I studied drugs of all classes. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions, including both the therapeutic effect and the toxic effects of drugs.

6. From December 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically within the health sciences group, and most of my projects dealt with issues surrounding products or processes regulated by the U.S. Food and Drug Administration (FDA). During my consulting career (ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I worked on a variety of projects pertaining to the regulation of products by the FDA, including human drugs, veterinary drugs, biologics, medical devices, consumer products, dietary supplements, and foods. I have advised clients, including drug manufacturers, on regulatory issues and strategies for their products, designed preclinical and clinical studies for both efficacy and safety, advised these clients on issues related to statements regarding efficacy and warnings for their products based on the current labeling regulations, and generally acted as a regulatory affairs staff for small companies in their early stages of product development. A tool common to all my work as a consultant is risk assessment, including many projects where risks and benefits of human medical products, including devices, are at issue.

7. With respect to my experience that is directly relevant to the issues in this case, my graduate training was in cardiovascular pharmacology and the drug at issue in this case, valsartan, is a cardiovascular drug product proved by FDA for the treatment of high blood pressure and heart failure. Thus, I am very familiar with the drug itself and the way is used by patients to treat chronic health conditions. I also have a great deal of experience in the care of genotoxic compounds and cancer risk assessment, human health concerns that are at the heart of this case with respect to the contaminants and impurities present in valsartan drug products. Finally, I have done a great deal of work on projects related to regulation of products by the FDA. Human prescription drugs are just one type of FDA-regulated product that my training and experience has included. Pharmacology (efficacy) and toxicology (safety) are core disciplines in terms of FDA regulation of human drugs. The work I have been involved with in my professional career has included work with manufacturers of both innovator drug products and generic drug products, both prescription and over-the-counter (OTC) drug products. I have been involved in preclinical and clinical development before marketing of a drug product as well as postmarket activities. I have performed safety assessments for companies involved in initial product development and provided strategic advice to companies in early-stage development. I have knowledge and experience with FDA regulations that govern the manufacturing of drugs as well, *e.g.,* compliance with Good Manufacturing Practice (GMP) and US Pharmacopeia (USP) standards. I have knowledge and expertise related to changes in the FDA regulations over the years from the initial passage of the Federal Food Drug and Cosmetic Act (FFDCA) in 1938 up to the most current amendments to the FFDCA (the Food and Drug Administration Reauthorization Act in 2017). This knowledge resulted from courses I have taken that were offered through the Food Drug and Law Institute (FDLI), experience while working at ENVIRON under the direction of former FDA employees, and experience gained while working as a consultant to industry since 1989.

8. As described in my curriculum vitae (attached to this report as Appendix A), I have lectured to graduate students, law students and pharmacy students on FDA regulations as they apply to human drug products, including lectures that have covered the FDA approval process, labeling of products, manufacturing standards, and post-market reporting requirements for drug manufacturers.

9. Throughout my career I have published dozens of articles which are listed in my curriculum vitae (Appendix A). In litigation, I have provided expert testimony and been qualified in both state and federal courts in the areas of pharmacology, pharmacokinetics, toxicology, risk assessment and FDA regulations, including the FDA regulations that relate to human drugs (Appendix B). Also attached to this report as Appendix C is a list of all documents I have reviewed in this case, in addition to or including documents referred to herein.

II. Summary of Key Opinions

- The carcinogenicity of NDMA has been understood for many decades and there is no controversy surrounding the fact that the compound is a potent carcinogen; an increased cancer risk is associated with exposure to nanogram levels of NDMA.
- Valsartan containing N-nitrosodimethylamine (NDMA) or N-nitrosodiethylamine (NDEA) was held out as being the generic equivalent of the FDA-approved branded drug listed in the Orange Book. This was not an accurate claim, however, because NDMA and NDEA are harmful impurities that are not listed under the branded pharmaceutical in the US Pharmacopeia (USP) valsartan monograph or the applicable valsartan FDA applications Abbreviated New Drug Applications (ANDAs).
- Diovan (the Reference Listed Drug "RLD" for valsartan) should not contain NDMA or NDEA.[1] Therefore, valsartan with NDMA or NDEA impurities are not pharmaceutically equivalent or therapeutically equivalent to the RLD due to the presence of NDMA or NDEA. Importantly, the presence of the NMDA and NDEA impurities meant the valsartan drug products were less safe than the RLD.
- Both active pharmaceutical ingredient (API) and finished dose drug manufacturers have an ongoing duty throughout the lifecycle of a drug product that includes the duty to perform adequate risk assessments and to develop and use suitable methods to detect impurities, including impurities present at low levels (i.e., nanogram levels) if the impurities are unusually potent, such as NDMA or NDEA.

[1] The is the case for all valsartan containing products, such as Diovan HCT (valsartan/hydrochlorothiazide), Exforge (valsartan/amlodipine), Exforge HCT (valsartan/amlodipine/hydrochlorothiazide), and Entresto (valsartan/sacubitril).

- At any point in time, valsartan manufacturers could have changed their processes to eliminate NDMA and NDEA impurities without prior authorization from the FDA.
- The lack of conformity with applicable cGMPs and the presence of nitrosamines in valsartan API and finished drug products rendered valsartan drug products adulterated as defined in FDA laws and regulations.

III. Information Reviewed and Methodology Employed

10. My work on this case has included a review of the following types of materials:

a) FDA regulations, guidance materials and other industry standards relating to human drugs of all types, including generic drug products, from initial development to approval to release into the marketplace and during marketing;

b) scientific literature and other documents related to strengths and weaknesses of current human drug regulatory system;

c) scientific literature and other relevant public information related to the toxicity of valsartan contaminants and impurities; and

d) confidential documents[2] produced during the litigation.

It should be noted that the sources listed above are ones commonly used in my work as a pharmacologist, toxicologist, regulatory consultant, and risk assessor. At the end of this report is attached a list of the published articles cited throughout this report. All opinions expressed in this report are expressed based on my training and experience and to a reasonable degree of scientific certainty.

11. With respect to the methodology I employed while working on this case and in forming my opinions as outlined in this report, I have used standard methods that I apply in all my work, both in litigation and non-litigation projects. One method I used is known in the industry as human health risk assessment. Scientists, like myself, who are involved in projects where the safety of drugs is at issue routinely assess both benefits and risks using the risk assessment process. Principles of pharmacology and toxicology are at the scientific core of risk

[2] The documents referenced here are one relating to the Defendants in this case which include Zhejiang Huahai Pharmaceutical Co. Ltd. (ZHP), Huahai US, Prinston Pharmaceutical Inc., Solco Healthcare US, Teva Pharmaceutical Industries, Ltd, and Torrent Pharmaceuticals.

assessment (Faustman and Omenn, 2013). Risk assessment has been used for decades by a wide variety of governmental bodies. In 1983, the National Research Council (NRC) detailed the steps for risk assessment and described the methodology that is in use today as four basic steps: hazard identification, dose-response assessment, exposure analysis, and characterization of risks (NRC, 1983). Each of the steps in a risk assessment involves assembly of available data or information, evaluation of the body of data and information, and the exercise of scientific judgement to draw conclusions about potential risks. As a result, risk assessment is a standard tool used in the scientific community and has been used in medical products to understand both the benefits and risks associated with a medical product, including drugs. Therefore, I used risk assessment as a tool when examining the risks associated with the exposure to contaminants and impurities in human drugs that are at issue in this case. Another method I employed in this case, singularly and in conjunction with risk assessment methods, is known as a "weight-of-the-evidence" assessment. A weight-of-the-evidence assessment involves evaluating individual studies or data and determining what the studies or data describe, when considered as a body of work.

12. I was trained in the use of these methods as part of my undergraduate, graduate, and postdoctoral work in pharmacology and toxicology, as well as while working as a consultant. Weight-of-the-evidence methodology, in particular, is used as part of regulatory decision making by regulatory and scientific bodies such as the FDA[3], the U.S. Environmental Protection Agency (EPA)[4], the U.S. Occupational Safety and Health Administration (OSHA)[5], the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC)[6]. The *Reference Manual on Scientific Evidence* also describes the use of weight-of-the-evidence by experts in the process of evaluating a body of data or studies[7]. Similarly, risk assessment methods are used by regulators when performing safety assessments for drugs, where both risks and benefits are assessed and weighed.

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[3] e.g., http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079257.pdf; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm074916.pdf; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079240.pdf.

[4] e.g., https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23160&CFID=65932199&CFTOKEN=24176705; https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=65932266&CFTOKEN=97071893.

[5] https://www.regulations.gov/document/OSHA-2016-0004-0002

[6] https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4971

[7] The *Reference Manual on Scientific Evidence, 3rd Edition*. National Research Council. 2011. Washington, DC: The National Academies Press. https://doi.org/10.17226/13163.

13. All opinions offered in this report are expressed to a reasonable degree of scientific certainty based on my training and experience in pharmacology, toxicology, and FDA regulation of human drugs. I reserve the right to supplement these opinions if additional information becomes available for review.

IV. Scope of Work

14. I have been retained by counsel for the Plaintiff in the above-referenced action to serve as an expert witness in the areas of the general toxicology of contaminants and impurities detected in valsartan, a human drug product used to treat high blood pressure and heart failure in humans, and the regulation of human drugs by the FDA. The regulatory opinions at this time are focused on the implications of the presence of contaminants and impurities in human drugs, and the regulations and industry standards that apply with respect to manufacturing of human drug products. As a toxicologist, I also was asked to provide opinions related to the human health risks associated with the presence of contaminants and impurities in a drug such as valsartan that is taken on a repeated basis by patients to treat chronic health conditions.

V. Regulation of Human Drugs in the US

15. Valsartan's manufacturing and marketing are regulated by the FDA (21 CFR Parts 200 through 499 in particular). FDA regulations pertain to the approval of new drug products, as well as the manufacturing and marketing of drugs once approved for human use. With respect to development of human drug products, the FDA does no testing itself. This means that the FDA does not conduct or monitor clinical trials, nor does the FDA choose the investigators involved in the clinical trials or the sites where the study is conducted. Instead, the FDA relies on drug companies to conduct all testing, both preclinical and clinical, and to provide the agency with the results of testing that is accurate and reliable, shows that the drug has therapeutic activity and is safe for use in humans. The FDA makes its decisions about drug approval and labeling based on the information provided by the applicant in its New Drug Application (NDA). A failure to provide all the safety information and related analyses that an applicant is aware of means that the FDA must make regulatory decisions based on incomplete information, decisions that could impact patient safety.

16. A specific regulatory category in the US is a "generic" human drug product. A generic drug is the same as a brand name drug product, sometimes referred to as the "innovator" drug, "in dosage, safety, strength, how it is taken, quality, performance, and intended use."[8] Before approving a generic drug product, FDA requires a company to perform a series of tests to assure that the generic drug can be "substituted" for the brand name drug. In other words, a physician can prescribe to patients, and a pharmacist can fill a prescription for, either the innovator drug product or the generic drug product and expect the patient to have the same therapeutic response, regardless of the drug product ingested. A company submits to FDA an application known as an Abbreviated New Drug Application, or ANDA. Like a NDA, the ANDA contains data that FDA reviews and evaluates during its premarket approval process. US law requires that a generic drug product contain the "identical amounts of the same active ingredient(s)" as the innovator drug product. The evaluation made by FDA establishes "therapeutic equivalence" between the generic drug product and the innovator product, where drug products evaluated as being "therapeutically equivalent" can be expected to have equal effect and no difference when substituted for the innovator product.

17. With respect to the preparation of an ANDA for a human prescription generic drug, Congress amended the FDCA in 1984 (Drug Price Competition and Patent Term Restoration Act) to establish approval pathways for drug products under section 505(j) of the FDCA and section 505(b)(2); the amendments also are known as the "Hatch-Waxman Amendments" to the FDCA. The amendments addressed patent term and exclusivity for generic drug products, including providing a 180-day exclusivity period for certain ANDA applicants. A 505(j) applicant is submitting an ANDA because the drug product at issue is a duplicate of a previously approved drug product; an ANDA relies on FDA's finding that the previously approved drug product, *i.e.,* the reference listed drug (RLD), is safe and effective. The regulations also require that the generic drug be the "same" as the RLD.[9]

[8] https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#G.

[9] FDA Generic Drugs: Questions & Answers, https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers ([a] generic drug is a medication created to be the same as an already marketed brand-name drug in dosage for, safety, strength, route of administration, quality, performance characteristics, and intended use."

18. Several terms or entities unique to the generic drug regulatory space have been mentioned, or will be mentioned, include "reference listed drug" or RLD, "suitability petition", "therapeutic equivalence", "bioequivalent/ bioequivalence", and the FDA Orange Book.[10] These are described below.

19. A "RLD" is defined by FDA as follows: *"A Reference Listed Drug (RLD) is an approved drug product to which new generic versions are compared to show that they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the Reference Listed Drug in its Abbreviated New Drug Application (ANDA). By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart."* The concept of a RLD is important in this case when generic drug versions of valsartan are compared to the innovator drug product known as Diovan (manufactured by Novartis Pharmaceuticals and first approved through an NDA[11] process in 1996 as a capsule and 2001 as a tablet).

20. A "suitability petition" is a request for permission *"to submit an ANDA for a generic drug product that differs from a RLD in its route of administration, dosage form, or strength, or that has one different active ingredient in a fixed-combination drug product (i.e., a drug product with multiple active ingredients)."*[12] Thus, FDA does permit certain differences between a proposed generic drug product and a RLD as long as the applicant submits to FDA, and gains approval of a "suitability petition" (see 505(j)(2)(C) of the FDCA; 21 CFR 314.93). In the petition the applicant requests permission to submit an ANDA that differs from the RLD in its route of administration, dosage form, strength, or it has one different active ingredient in a fixed-combination drug product. The suitability petition must be approved before an ANDA citing a suitability petition is submitted to FDA. Such petitions are not at issue in this case.

[10] The definitions can be found at https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms/.
[11] NDA 021283 information can be found at: https://www.accessdata.fda.gov/scripts/cder/daf/indeX.cfm?event=overview.process&ApplNo=021283.
[12] https://www.fda.gov/media/86656/download.

21. FDA has stated that approved generic drug products are "therapeutic equivalents" if they are pharmaceutical equivalents for which bioequivalence has been demonstrated, and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[13] As a result, therapeutic equivalents can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Thus, drug products are deemed therapeutically equivalent only if they are pharmaceutical equivalents (contain the same active ingredient(s); dosage form and route of administration; and strength). Since "therapeutic equivalent" and "pharmaceutical equivalent" are dependent upon each other in terms of FDA assessment, FDA also specifically defines pharmaceutical equivalents as follows:

> *"Pharmaceutical Equivalents. Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where the residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. They may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, within certain limits, labeling."*

Thus, a new version of valsartan must meet identity, strength, quality, and *purity* standards. Valsartan that contains the impurities NDMA or NDEA does not meet the quality or purity standards to be considered pharmaceutically equivalent or therapeutically equivalent to the RLD.

22. As described by FDA, "bioequivalence" is a statutory term FFDCA Section 505(j) (21 U.S.C. 355(j)); ANDA applicants must demonstrate that *"the proposed generic product is*

[13] https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.

bioequivalent to its reference listed drug."[14] The term is defined in the FDA regulations (21 CFR 320.1 referencing 21 CFR 314.3): *"The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."*

23. The "FDA Orange Book" is a resource that was put into place by the agency to satisfy a requirement of the 1984 Hatch-Waxman Amendments. The 1984 amendments require FDA to make publicly available a list of approved drug products with monthly supplements; the Orange Book[15] and its monthly Cumulative Supplements satisfy this requirement. The Orange Book identifies drug products approved based on safety and effectiveness by the FDA under the FDCA and related patent and exclusivity information.

24. Unlike innovator drug products, applications for generic drug products do not require development of large amounts of efficacy and safety data. Instead, the FDA describes the information required as follows:

> *"There are several types of data generic companies must submit to us for review and evaluation. For one, it is critical that the data show the manufacturing process – how the generic drug will be made by combining the active ingredient, which really provides the treatment, and the inactive ingredients. These data let us know if the manufacturer can reliably make a high-quality product.*
>
> *The company must also show its generic product will behave the same way in patients as the brand-name product. To prove this, the company is often required to conduct studies with human volunteers who take both the brand and generic drug products. FDA compares the data from these trials to validate that the generic drug is safe, effective and can be substituted for the brand-name product. Patients should be able to take the brand-*

[14] https://www.fda.gov/files/drugs/published/Bioavailability-and-Bioequivalence-Studies-Submitted-in-NDAs-or-INDs-%E2%80%94-General-Considerations.pdf.
[15] https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book; https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.

name drug on one day and the generic drug on another day and receive the same treatment effect.

So basically, manufacturers have to prove the active ingredient is the same as the brand-name drug that is being copied. The manufacturers also must show that the right amount of the active ingredient goes to the place in the body where it has an effect, and any inactive ingredients used are safe. Companies need to show that the drug will not deteriorate over time, that the manufacturer can produce the same drug every time, and that the labeling is the same as for the brand-name drug."[16]

Thus, the only clinical data typically required for orally administered small molecules are data in healthy volunteers relating to the rate and extent of absorption of the generic drug product as compared to the rate and extent of absorption for the innovator drug product (Chow, 2014). This process is called demonstrating "bioequivalence".

25. In this case, it is important to understand the role of the US Pharmacopeia (USP). The United States Code (USC), Title 21, Chapter 9, subchapter V, part A section 351 (adulterated drugs and devices; also referred to as 21 USC 351) is a section of US drug law that addresses what makes a drug "adulterated". In the section it is stated as follows:

"A drug or device shall be deemed to be adulterated (351) (a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture (1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or (2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; ***or (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess****; …" [emphasis added]*

[16] https://www.fda.gov/drugs/news-events-human-drugs/generic-drug-approval-process.

Valsartan with NDMA or NDEA impurities does not meet the quality or purity characteristics which it purports, or is represented, to possess and therefore would be deemed adulterated. Also discussed in this section is the fact that "official compendia" exist for certain drugs. One such "official compendium" identified is the USP. In the case of valsartan, valsartan/hydrochlorothiazide, and amlodipine/valsartan/hydrochlorothiazide the USP has a published monograph available (ZHP01303141; ZHP02614594; PRINSTON00141349; TEVA-MDL2875-00157195).

26. As an organization, the USP sets quality standards for drugs, both active ingredients and excipients; the USP has set over 5000 such standards for drugs, both chemically synthesized (like valsartan) and biologically derived products. USP standards exist to ensure *"the quality of medicines and their ingredients, and to protect the safety of patients."*[17] Regulatory authorities around the world recognize USP standards and, in the US, the standards reflect the attributes of drug products approved by the FDA. The monographs specify the identity, strength, purity, and performance of the drug product and describe tests to validate that a medicine and its ingredients meet these criteria. If a process results in impurities not listed in the USP, testing methods not listed in the USP may be necessary to ensure the drug product is free of harmful impurities, such as NDMA or NDEA.[18] Defendants Prinston and ZHP recognized this, noting in an ANDA submission: *"There is a USP method for testing other related compounds in the drug substance monograph. However, the USP method was not acceptable because it could not completely resolve other potential impurities."* (ZHP01451842 at 855). In addition to individual USP monographs, USP has standards that address general issues around drug quality (https://www.usp.org/). USP updates its standards and general procedures information as new procedures become available. The USP does not list impurities for which there is no acceptable amount allowed in the drug product, such as with NDMA or NDEA. The USP states the following regarding nitrosamine impurities, "To ensure drug product

[17] https://www.usp.org/about/public-policy/overview-of-monographs.

[18] USP 38 General Notices and Requirements 5.60 Impurities and Foreign Substances "Tests for the presence of impurities and foreign substances are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also Impurities in Drug Substances and Drug Products <1086>). Nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the test provided in the individual monograph, where the presence of the impurity is inconsistent with applicable good manufacturing practices or good pharmaceutical practice."

quality, manufacturers must properly assess the risk of nitrosamine formation in their products and further investigate any potential risks."[19]

27. As part of the ANDA process at FDA, companies submitting the ANDA are allowed to reference something called a "Drug Master File" or DMF. As described by FDA:

> *"Drug Master Files (DMFs) are submissions to FDA used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drug products. They:*
>
> - *Allow parties to reference material without disclosing DMF contents to those parties.*
> - *Are not required by statute or regulation.*
> - *Are neither approved nor disapproved. Instead, FDA reviews the technical contents of DMFs in connection with the review of applications that reference them (e.g., NDAs, ANDAs, INDs, BLAs)."*[20]

There are some important features of the process of reference to a DMF that impact the responsibilities of companies making generic drug active pharmaceutical ingredients (APIs) or finished drug products. For example, 21 CFR 314.420(a) explains what happens when a DMF is referenced by a company. The regulations state:

> *"(a) A drug master file is a submission of information to the Food and Drug Administration by a person (the drug master file holder) who intends it to be used for one of the following purposes: To permit the holder to incorporate the information by reference when the holder submits an investigational new drug application under part 312 or submits an application or an abbreviated application or an amendment or supplement to them under this part, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person.* ***FDA ordinarily neither independently reviews drug master files nor approves or disapproves submissions to a drug master file.*** *Instead, the agency customarily reviews the information* ***only in the context of an application under part 312 or this part****." [emphasis added]*

[19] https://www.usp.org/small-molecules/nitrosamine-impurities.
[20] https://www.fda.gov/drugs/forms-submission-requirements/gdufa-ii-drug-master-files-dmfs.

This issue of FDA "approval" of a Drug master File is further explained by FDA in a guidance document: *"A DMF is NOT a substitute for an IND, NDA, ANDA, or Export Application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, ANDA, or an Export Application."*[21] In other words, FDA does not "approve" a Drug Master File submission, or a change or amendment to a Drug Master File (see slide 31 of FDA, 2013[22]). Instead, the agency does a technical review of the DMF and any amendments only in the process of undertaking some type of regulatory review action such as review of an ANDA that refers to the DMF. The approval is for the product subject to the ANDA filing under review, not for the DMF process (FDA regulates products, not processes[23]). Importantly with respect to DMFs, DMF holders are required to *"notify affected authorized parties of any DMF changes, additions, or deletions (§ 314.420(c)) and should provide sufficient information to enable authorized parties to determine the appropriate reporting procedure for their applications (see §§ 314.60, 314.70, 314.96, and 314.97). This notification should occur well before making any changes to permit authorized parties to report application changes within an appropriate time frame."*[24] In this case, the Drug Master File in question was held by Zhejiang Huahai Pharmaceuticals (hereafter referred to as "ZHP"). It is the responsibility of drug companies to conduct the necessary analysis and risk assessments for their product to determine how, and in what ways, proposed changes in the API process might affect their product's impurity profile. ZHP's inadequate risk assessment led to ZHP incorrectly concluding that utilizing zinc chloride and dimethylformamide had "a lower risk in terms of quality and safety" (ZHP01843066 at 099; PRINSTON00077339 at 342) and classifying the change as a minor change in their DMF change request (ZHP01843066 at 116). However, ZHP's change to utilize zinc chloride and dimethylformamide was internally classified as a critical change (ZHP01843066 at 067). The FDA noted the following in an Establishment Inspection Report (EIR) to ZHP (ZHP01840846 at 847):

> *"Additional testing requirements associated with critical changes are not always based on sound scientific judgment. Change Request PCRC-11025 included changing both the catalyst and the solvent in your validated manufacturing process. Additional testing*

[21] https://www.fda.gov/drugs/guidances-drugs/drug-master-files-guidelines.
[22] https://www.fda.gov/media/85079/download.
[23] https://www.fda.gov/about-fda/fda-basics/what-does-fda-regulate.
[24] https://www.fda.gov/media/131861/download.

requirements associated with these changes were limited to three validation batches and a commitment to conduct additional testing on three batches a year.

You do not have an adequate classification procedure for determining the level of testing, validation, and documentation needed to justify changes to a validated process. You do not consistently classify changes. You do not always increase testing, validation, and the documentation required to justify changes to a validated process based on the classification of a proposed change. Amendment to Drug Master File Valsartan USP (process II) DMF# 23491 dated December 10, 2013 indicates the amendment was submitted for minor changes for drug substance manufacturing. Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 contradicts your internal Change Request PCRD-11025 which lists change control classification as critical change."

28. In addition to the submission of an ANDA itself, other types of submissions may be made by ANDA holders to supplement their approved applications. In 1997, the Food and Drug Administration Modernization Act was passed into law and Section 116 of the Modernization Act amended the FDCA by adding section 506A. This section provided requirements for making and reporting manufacturing changes to an approved NDA or ANDA and for distributing a drug product made with such changes. The changes to the law were codified in 21 CFR 314.70 and guidance related to both NDA and ANDA holders[25] was made available in 2004. With these changes, FDA set forth categories of changes (minor changes, moderate changes and major changes) that differ based on the risks associated with such changes in terms of impacts on safety and/or efficacy. A major change to an ANDA has been defined in FDA's guidance as *"a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product."* Such changes require submission of a Prior Approval Supplement (PAS) as well as approval by FDA of the PAS before distribution of the drug product made using the change. A moderate change is defined as *"a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug*

[25] https://www.fda.gov/files/drugs/published/Changes-to-an-Approved-NDA-or-ANDA.pdf.

product." Such changes require submission of a Supplement-Changes Being Effected (CBE) document, either a CBE-30 or a CBE. A drug product that is subject to a CBE-30 supplement because of a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required. For a drug product subject to a CBE supplement because of moderate changes, distribution can occur when FDA receives the supplement. A minor change to an ANDA is defined as *"a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product."* The ANDA holder in this case can describe minor changes in its next Annual Report instead of submitting a supplement. In all these cases, it is the responsibility of the ANDA holder to choose the proper type of supplement to make to its ANDA. At any point in time the valsartan ANDA holders could have implemented numerous changes that would have eliminated the potential for NDMA and NDEA formation without first obtaining authorization from the FDA, such as returning to the original process in the Drug Master File that did not produce NDMA or NDEA or testing for the presence of NDMA and NDEA and not selling drug product containing NDMA or NDEA. In 2019, ZHP stated the following after investigating the cause of NDMA and NDEA in their valsartan API (ZHP01634739 at 932-933):

> *"The step that will most likely generate NDMA is the crude step of Process ($ZnCl_2$) where dimethylformamide and nitrous acid exist simultaneously to render the nitrosation reaction to proceed. In addition, since the quenching takes place in the presence of the product, trace amount of NDMA formed during the quenching step could be present in that product and may also be carried over into the final product. Based on this elucidated root cause, the presence of trace amount of NDMA in the final Valsartan drug substance requires the convergence of the following three factors: i) use of dimethylformamide, ii) quenching of azide using nitrous acid, and iii) quenching takes place in the presence of the product. In other words, lack of any one of the three factors above can avoid the formation of NDMA in the current drug substance.*
>
> *From the process perspective,* ***the easiest way to avoid the formation of NDMA in the current drug substance process is to change Factor iii, i.e., to perform the quenching without the presence of the product. This optimization can be achieved rather easily*** *by*

separating the organic phase (containing the product of the step) from the aqueous waste (containing unreacted azide) and then performing quenching only on the aqueous waste; therefore, any formation of NDMA will not be carried over into the product. ***This approach can be done without change of manufacturing process****."*

*****

"N-Nitrosodiethylamine is potential process-related impurity, which has a similar formation mechanism as NDMA. It is most likely generated in terminated TEA process with NaNO2 quenching, in which TEA-HCl (containing potential impurity of diethylamine) and nitrous acid exist simultaneously to render the nitrosation reaction to proceed. In current separated quenching process, no source of diethylamine is introduced and the any possible generation of nitrosamines can be minimized if the aqueous waste phase is separated from the organic phase. So the risk of NDEA is considered to be extremely low." [emphasis added]

At any point in time, ZHP could have, without FDA authorization, changed their process as they indicate later in 2019 (i.e., quenched outside the presence of the drug product) and ANDA holders could have sold valsartan finished dose utilizing valsartan API quenched outside the presence of the drug product, resulting in the sale of valsartan finished dose without the presence of NDMA or NDEA impurities.

29. In the current case, two important terms related to regulatory compliance and/or compliance with standards such as a USP monograph are "impurity" and "contaminant". Before discussing any of the guidance or standards that exist and are applicable to this case, these terms are important to distinguish from one another. An "impurity" will be defined consistent with how it is defined in FDA guidance and regulations. It is a substance that is detected in a drug product and is present because of the chemical process used to make the drug or a degradation product due to storage of the drug.[26] In contrast, a "contaminant" is something found in a drug product that comes from external or extraneous sources and not due to the nature of the process used to make a drug or storage of the drug.[27] With regard to ZHP, the NDMA and NDEA found in their

[26] https://www.fda.gov/media/71727/download.
[27] https://www.fda.gov/media/71727/download.

valsartan API would primarily be considered impurities, because the NDMA and NDEA were the result of the chemical process utilized.

30. Since a generic drug product must be the "same" as the RLD, one of the requirements applies to impurities in the drug products. FDA has issued guidance on this topic (1999 guidance[28]) and makes recommendations for including information in ANDAs and supporting Drug Master Files on the identification and qualification of impurities in drug substances produced by chemical syntheses for both monograph and non-monograph drug substances. Three types of impurities are described: organic impurities (process and drug related); inorganic impurities; and residual solvents. In this 1999 guidance, FDA stated with respect to organic impurities: *"Identification of impurities below apparent levels of 0.1 percent is generally not considered necessary.* ***However, identification should be attempted for those potential impurities that are expected to be unusually potent, producing toxic or pharmacologic effects at a level lower than 0.1 percent.****" [emphasis added]* The organic impurities detected in the valsartan drug products at issue in this litigation will be discussed later in this report. It also is important to note that FDA recognized the fact that the qualitative impurity profile of the drug substance may change, or a new impurity may appear. Thus, drug manufacturers have a duty to ensure that the impurity profiles of generic drug products, even after initial approval, do not change over time, particularly when chemical processes may change, even in very small ways. This is consistent with FDA's 2004 guidance on ANDA manufacturing changes. With respect to this case, Dr. Min Li of ZHP agreed during his deposition that conducting a risk assessment is an ongoing process during the lifecycle of the drug substance (see page 233 of Dr. Min Li's deposition dated April 20, 2021). Furthermore, Dr. Li agreed that the technology and methodology was clearly available to identify NDMA (see page 230 of Dr. Li's deposition).

[28] FDA, 1999.

31. In addition to the 1999 FDA guidance on impurities in generic drugs, the International Conference on Harmonization (ICH)[29] has published guidance on this topic as well (ICH Topic Q 3 A (R2): Impurities in new Drug Substances). A review of that guidance shows that the information provided closely tracks with the 1999 FDA guidance on the topic.

32. In 2014, as part of its ongoing modernization initiatives, USP began the process to update its chapters on drug impurities, specifically the chapter known as *Impurities in Drug Substances and Drug Products* [1086]. At that time, USP was proposing that a new chapter be developed to address organic impurities testing for monograph articles, including the United States Pharmacopeia–National Formulary (*i.e.,* valsartan is part of the National Formulary). As the USP stated in 2014:

> *"This new chapter has been created to align with current scientific and regulatory approaches and* ***to help ensure the appropriate control of organic impurities and degradation products in drug substances and drug products****. The goal is to provide a science-based approach for the control of impurities in relevant monographs, and thereby to ensure the quality of the product as it relates to safety and efficacy." [emphasis added]*

Of particular importance is the fact that the 2014 document references the situation that is relevant in this case: *"When a detected impurity is not described in the individual monograph,* ***the manufacturer is responsible*** *for developing appropriate specifications (analytical procedures and acceptance criteria)."* Thus, drug manufacturers are responsible for detecting unknown impurities and identifying the unknown impurities once detected. For instance, an unknown impurity could be detected when an unknown peak appears in a chromatogram. Once an unknown peak is detected, the manufacturer is also responsible for identifying the corresponding unknown impurity. After placing ZHP on import alert, the FDA reiterated that the detection and identification of impurities is the responsibility the of manufacturer (TEVA-MDL2875-00641067):

[29] See the ICH website: *"The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines. Since its inception in 1990, ICH has gradually evolved, to respond to increasingly global developments in the pharmaceutical sector and these ICH guidelines are applied by a growing number of regulatory authorities. ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards.*

"FDA placed Zhejiang Huahai Pharmaceuticals on import alert on September 27, 2018, to protect U.S. patients ***while the active pharmaceutical ingredient (API) manufacturer fully determines how impurities were introduced into its API and remediates its quality systems****. The import alert stops all API made by ZHP and finished drug products made using ZHP's API from legally entering the United States. FDA's action follows a recent inspection at ZHP's facility.*

FDA reminds manufacturers that it is their responsibility to develop and use suitable methods to detect impurities, including when they make changes to their manufacturing processes. If a manufacturer detects new or high levels of impurities, they should fully evaluate the impurities and take action to ensure the product is safe for patients.*" [emphasis added]*

Evidence in this case also shows that in a November 29, 2018, Warning Letter to ZHP, the FDA found that ZHP did not meet their responsibility to detect impurities in their valsartan API (ZHP01344159):

"In November 2011 you approved a valsartan API process change (PCRC – 11025) that included the use of the solvent DMF. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, ***you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process****. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine. According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.*

You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing and making changes to,

> ***your manufacturing processes***. *If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.*
>
> *Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that* ***you are responsible for the quality of drugs you produce****." [emphasis added]*

33. An important issue in this case is the fact that the impurities and contaminants found in valsartan drug products are compounds that are known human carcinogens and/or are genotoxic compounds. The ICH process has addressed this special class of organic impurities (June 2015: *ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*). The final ICH step was achieved in 2018 and that led to the publication of the document that addresses the issue of DNA reactive impurities in pharmaceuticals. As stated in the document, its purpose *"... is to provide a practical framework that is applicable to the identification, categorization, qualification, and control of these mutagenic impurities to limit potential carcinogenic risk. This guideline is intended to complement ICH Q3A(R2), Q3B(R2) (Note 1), and ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorizations for Pharmaceuticals."*

34. Although other experts in this case are specifically addressing compliance with Good Manufacturing Practices, often referred to simply as "GMPs" or current GMPs (cGMPs), as someone who practices in the area of compliance with FDA regulations, it is important to mention what the regulations related to manufacturing require and why compliance with the regulations is important to ensuring the drugs are both safe and effective for use in patients. The FDA regulations in section 21 CFR 210 and 211 provide the framework within which human prescription drugs that are produced by chemical synthesis (both NDA and ANDA drug products) must operate in order to manufacture compliant products (Bowerstock and Vincins, 2019). The FDA regulations in this area require the establishment of a Quality Management

System (QMS) within companies where the system guides and documents all activities within the company and maximizes the likelihood that full compliance will be achieved. Any company that manufactures a human drug product is expected to have a QMS in place. Inspections by FDA focus on all elements of a company's QMS. Included in a QMS is documentation for all parts of the manufacturing process including internal policies, detailed work instructions, and detailed records to provide evidence of compliance. As stated in a recent textbook on the US regulatory system for therapeutic products (Bowerstock and Vincins, 2019):

> *"FDA CGMPs exist to ensure safety and effectiveness of all pharmaceutical, biologic, and medical device products manufactured and commercialized in the US. The importance of compliance with these regulations cannot be minimized. Quite simply, failure to adhere to CGMP requirements results in adulterated product that puts public health at risk. Compliance with CGMP regulations is the responsibility of every manufacturer that commercializes pharmaceutical, biologic, medical device, and combination products in the US."*

35. ANDA holders and companies manufacturing either active pharmaceutical ingredients (APIs) and/or finished drug products must comply with cGMPs and are subject to inspections by FDA (21 CFR Part 210 and 211). Insight into the FDA process for an inspection by FDA are available as well (https://www.fda.gov/media/75201/download; https://www.fda.gov/media/75167/download). Importantly, in FDA guidance on the issue of *Contract Manufacturing Arrangements for Drugs: Quality Agreements* (FDA, 2016), the agency explicitly points out who is legally responsible for quality when a company may use a contract manufacturer (in this case an API manufacturer for a generic drug product would be such contractors for an ANDA holder). FDA states:

> *"FDA's regulations recognize that owners commonly use contract facilities to perform some drug manufacturing activities.* ***When an owner uses a contract facility, the owner's quality unit is legally responsible for approving or rejecting drug products manufactured by the contract facility, including for final release****. The regulations*

require that the quality unit's responsibilities and procedures be in writing and that they be followed."[30] *[emphasis added]*

Thus, even if an API manufacturer bears responsibility for GMP compliance, the ANDA holder is still the ultimately responsible entity in terms of ensuring drug quality; quality is a critical component of safety.

36. In the period before drug approval by the FDA, premarket, the adequacy of a drug's label is assessed as part of the normal drug approval process for a NDA or a Supplemental New Drug Application (sNDA), as well as an ANDA. Thus, the drug approval process includes FDA approval of the drug's proposed labeling. In the post-marketing period for human prescription drug products, the FDA enforces this part of the regulations when they become aware of information, through either the drug manufacturer or through other sources, showing that the risk profile of the drug has changed, or that the use patterns of the drug have changed. It is important to note that even though ANDA holders have been required to mimic the labeling of the innovator drug product, if a generic drug manufacturer becomes aware of a patient safety concern that is not included in the current drug labeling for their product, they still have the duty to notify FDA of the patient safety issue (21 CFR 314.98). The company always can request FDA consider a label change, particularly in cases where the patient safety information is not currently in the product labeling or there is a need to strengthen the warnings in the label. In addition, 21 USC § 352(a) requires that a drug's labeling not be "false or misleading in any particular." FDA decisions about whether a drug's label is false or misleading often will depend on a manufacturer providing the agency with complete, accurate and timely information that they are aware exists and would impact the safety and/or efficacy of its drug.

37. It often is not appreciated that FDA's ability to ensure that human drugs marketed and sold in the US are safe for use by patients are affected by some of the inherent limitations of agency resources. These FDA limitations have been discussed in a variety of reports authored by independent bodies such as the National Academy of Sciences, Institute of Medicine (IOM) and

[30]https://www.fda.gov/media/86193/download#:~:text=A%20quality%20agreement%20is%20a,each%20will%20comply%20with%20CGMP.

the General Accounting Office (GAO). For example, the IOM published its findings in 2007[31] of a review and analysis the FDA's drug safety system and programs. The review had been requested by FDA itself that the IOM examine in detail the system of drug safety in the US. As the report itself stated:

> *"Although the agency has gained great respect and importance as one of the world's premier regulatory bodies, recent drug safety events have called into question FDA's regulatory decision-making and oversight processes and caused the public to question its ability to accomplish a balanced evaluation of the safety and efficacy of the drugs it reviews and after their approval, of their performance under real-life conditions."* [see page ix in the Preface]

As a result of their review, the IOM made a series of recommendations aimed at improving the drug safety system through measures such as *"strengthening clinical and epidemiological research, and the scientific basis of regulatory action."* This review clearly outlines limitations in the FDA system (*e.g.,* organizational challenges that lead to dysfunction; inadequacies in the regulatory framework in terms of ensuring drug safety). Yet, in a 2007 publication, the FDA response to the IOM analysis a report was criticized (Smith, 2007). As stated in the article:

> *"Sadly, the FDA's official response [to the IOM report] falls far short of what the American public expects and deserves. Indeed, it highlights the very reason that the agency — with which I have had some firsthand experience— is in need of monumental change: its philosophy is no longer aligned with its regulatory mandate."*

Other assessments of FDA's limitations in terms of ensuring the safety of the drug supply in the US have been performed by the General Accounting Office (GAO), The GAO has authored two recent reports that focused on the limitations of the FDA oversight with respect to foreign drug suppliers.[32] As the GAO discusses in their reports, FDA has lacked complete and accurate information on foreign drug manufacturing establishments, information critical to ensuring patient safety. In 2022, GAO made three recommendations including *"that FDA incorporate leading practices into the design of both its unannounced inspection and translation pilot programs and fully develop tailored strategies to ensure it has a sufficient foreign inspection workforce."* Given that many generic drug products are manufactured by foreign facilities, these

[31] See GAO-11-936T and GAO-22-103611.
[32] See GAO-11-936T and GAO-22-103611.

limitations would be of particular concern to this industry and the products they market and sell in the US.

38. Regulatory actions related to drug safety issues can result in the issuance of "Warnings Letters" by FDA. As discussed by FDA in its Regulatory Procedures Manual[33]: *"It is the Food and Drug Administration's (FDA's) practice to give individuals and firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. Warning Letters are issued to achieve voluntary compliance and to establish prior notice. The use of Warning Letters and the prior notice policy are based on the expectation that most individuals and firms will voluntarily comply with the law.*" Warning Letters are often issued after FDA compliance inspections of manufacturer facilities when inspectors have identified situations where the violations are of regulatory significance, where FDA defines significant violations or those violations that may lead to enforcement action if not promptly and adequately corrected. Therefore, issuance of Warning Letters are important actions by FDA as they are providing a manufacturer with notice of corrections or changes that need to be made by the company.

39. A tool that is available for providing important patient safety information directly to healthcare systems and physicians about drugs is a written communication known as a "Dear Doctor" letter or "Dear Healthcare Provider" letter. FDA has recognized the usefulness of such communications related to all types of medical products, including human drugs.[34] Therefore, manufacturers can communicate directly with physicians when there is important patient safety information to convey. FDA also has the authority to communicate directly with the public about drug safety issues it identifies. This means that in cases where a manufacturer of a drug product identifies a patient safety concern that has not been discussed fully in the product's label or identifies a new type of safety concern related to use of the drug, a company, including a ANDA holder, always can directly inform physicians without waiting for FDA to act to initiate a label change.

[33] https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf.
[34] https://www.fda.gov/media/102575/download.

VI. Toxicology of Nitrosamines Detected in Valsartan Drug Products

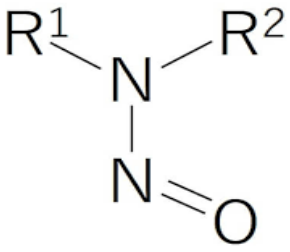
40. At issue in this case is the presence of impurities and contaminants in valsartan drug products that were manufactured in foreign countries, sold in the US, and were approved under a ANDA process by FDA. The impurities and contaminants of concern fall into a class of chemicals known as "N-nitroso compounds" and further classified as either "nitrosamines" or "nitrosamides". The toxicology of N-nitroso compounds has been known for decades and is even described in textbooks (*e.g.,* Williams and Weisburger, 1991. Chemical carcinogenesis. In: *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 4th edition, chapter 5, Pergamon Press: New York, pp. 127-200; and later editions of this same textbook up to the most recent 9th edition). As described in 1991:

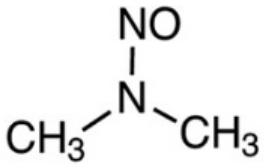
> *"N-nitroso Compounds. This major class of important chemical carcinogens is characterized by chemical derived from secondary amines or amides by nitrosation. Nitrosamines an nitrosamides are synthetic as well as naturally occurring substances, They were discovered to be carcinogenic only in the last 35 years beginning with the findings of Barnes and Magee om England that dimethylnitrosamine, an industrial solvent that caused jaundice and liver damage in workmen exposed to it, was highly hepatotoxic in rodents where it reproduced lesion seen in humans, Subsequently they demonstrated that this chemical was among the most carcinogenic chemicals then known. Some of the first studies on alteration of DNA by carcinogens were performed with nitrosamines and their patterns of alkylation of DNA have now been extensively documented."*

As already mentioned in this report, two specific N-nitroso compounds are of particular concern, NDMA and NDEA. It should be noted that NDMA is another name for the compound mentioned in the 1991 textbook, *i.e.,* dimethylnitrosamine. Thus, the carcinogenicity of NDMA has been understood for many decades and there is no controversy surrounding the fact that the compound is highly potent as a carcinogen.

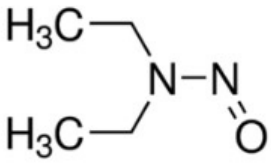
41. The chemical structures of NDMA and NDEA are as follows[35]:

Core structure[36] for NDMA and NDEA





NDMA Structure



NDEA Structure

Inspection of the structure of these two compounds show their similarity.

42. Both compounds, in fact, have been classified as carcinogens by various regulatory or authoritative bodies. Both NDMA and NDEA were classified as carcinogens by the National Toxicology Program (NTP) in 1981.[37] The classification was part of the Report on Carcinogens (RoC) program at NTP. The RoC is a congressionally mandated (1978 inception), science-based public health document that NTP prepares for the HHS Secretary on a routine basis based on nominations of compounds for review; there have been 15 RoC reports produced to date, the first one issued in 1980. The N-nitroso compounds NDMA and NDEA were evaluated and listed in the second RoC in 1981. In 1981, the NTP concluded for NDMA: *"N-Nitrosodimethylamine [NDMA] is reasonably anticipated to be a human carcinogen based on*

[35] Images of the individual compounds taken from https://www.shionogi-ph.co.jp/en/introduction/nitrosoamine.html.
[36] Image taken from: https://www.eurofins.co.jp/eurofins-biopharma-product-testing-kyoto/services/impurity-testing/nitrosamine-testing/.
[37] https://ntp.niehs.nih.gov/ntp/roc/content/profiles//nitrosamines.pdf.

sufficient evidence of carcinogenicity from studies in experimental animals." For NDEA, the NTP concluded: *"N-Nitrosodiethylamine [NDEA] is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals."* It should be noted that the NTP is part of the Department of Health and Human Services within the US government; FDA also is part of the Department of Health and Human Services. In my experience, activities of the NTP, such as the RoC reports, are well-known in the medical products industry, including the drug industry.

43. In addition to the NTP, the International Agency for Research on Cancer (IARC) had identified both NDMA and NDEA as carcinogens, but earlier than NTP (in 1972). With respect to NDMA, the IARC evaluation statements are important to consider:

> *"N-Nitrosodimethylamine (DMN) [NDMA] is carcinogenic* ***in all seven animal species tested.*** *The main target organs are the liver and the kidney. It induces tumours* following different routes of administration, including ingestion *and inhalation. It is carcinogenic following* ***prenatal exposure and in single-dose experiments****. Similarities in metabolism in human and rat liver tissues have been reported." [emphasis added]*

Then, with respect to NDEA, IARC stated in 1972:

> *"N-Nitrosodiethylamine (DEN) [NDEA] is carcinogenic i****n all ten animal species tested, including sub-human primates****. The main target organs are the nasal cavity, trachea, lung, oesophagus and liver. It induces tumours following* ***different routes of administration, including ingestion****, inhalation and skin painting. It is carcinogenic in* ***single-dose experiments and following prenatal exposure****." [emphasis added]*

The fact that as early as 1972 it was known that both NDMA and NDEA were potent carcinogens, having the ability to induce cancer in animals after single doses and following prenatal exposures, is important to any human health analysis, including analyses related to the presence of impurities or contaminants in human drugs that would be ingested repeatedly (chronic exposures likely) by patients. In other words, Defendants knew or should have known about the human health concerns regarding *N*-nitroso compounds that were either present, or could be formed, during the chemical synthesis of valsartan.

44. In fact, evidence in this case shows that Defendants could or should have had some knowledge about the risk of *N*-nitroso compound formation and the presence of the general class of nitrosamine impurities in valsartan. As background, ZHP developed several different chemical processes over time for production of valsartan as an API. ZHP's initial Drug Master File (DMF 020939; filed September 2007[38]) described a process that was similar to the process used for production of Diovan and is referred to in deposition testimony as the "tin process" due to the use of tributyl tin chloride in the reaction. Dr. Hecht, an organic chemist and expert in this litigation states in his report[39] that the tin process without quenching is not associated with a risk of formation of nitrosamine impurities. The tin process was replaced by ZHP, however, with processes that carried the risk of formation of nitrosamine impurities; one process has been referred to in depositions and documents as the "TEA process" (TEA is an abbreviation for triethylamine) and another has been referred to as the "$ZNCl_2$ process" ($ZNCl_2$ is an abbreviation for zinc chloride). ZHP's Drug Master File for valsartan production that is relevant in this case in terms of production of nitrosamine impurities was DMF 23491 and it is the Drug Master File that describes both the TEA process and the $ZNCl_2$ process. These processes and their link with the likely formation of nitrosamine impurities, in particular NDMA and NDEA, are described in detail in the report of Dr. Hecht.

45. The deposition testimony of Dr. Eric Gu, President/General Manager of Shanghai Syncores, a company owned by ZHP, indicates that one of the valsartan manufacturing processes that was used by ZHP (DMF 23491), the $ZNCl_2$ process, employed the solvent dimethylformamide, also often referred to in documents as "DMF" (not to be confused with use of DMF to abbreviate the regulatory term Drug Master File). Yet, it had been known in the chemistry community at least by 2009 that diemthylformamide can decompose and form dimethylamine; dimethylamine formation can lead to formation of NDMA in the presence nitrous acid (see pages 172-183 of Eric Gu's deposition dated April 5, 2021). Dr. Gu also testified that the Syncores and ZHP research and development activities related to valsartan chemical synthesis failed to apply core principles of the ICH guidelines related to identification of impurities in chemical reactions (see pages 244-247 of Eric Gu's deposition dated April 5,

[38] PRINSTON00078386.
[39] Dr. Stephen Hecht's July 6, 2021 Expert Report.

2021). ICH core principles relate to the investigation of all potential degradation products of chemical reactions (*e.g.,* ICH Q3A). In the context of cGMP compliance, these core principles related to identifying potential degradation by-products/ impurities is part of the risk assessment that drug manufacturers are expected to perform. The lack of full evaluation of its chemical processes also has been stipulated to by Defendants (see document entitled *"STIPULATION OF ZHEJIANG HUAHAI PHARMACEUTICAL CO., LTD."*; dated May 13, 2022). As a result of ZHP's inaction with respect to the ICH core principles and its duties as a human drug manufacturer under FDA regulations, ZHP failed to identify the potential of their process to lead to formation of NDMA and/or NDEA. It should be noted that all ANDA holders have a responsibility to either perform such risk assessments or to ensure that such risk assessments have been performed for any API they may incorporate into their finished drug products. In this case, the duty to ensure purity of their drug products applies to ZHP, Prinston, Teva, and Torrent.

46. ZHP's deputy director of technical affairs, Dr. Peng Dong, confirmed that ZHP failed to perform a risk assessment for potential decomposition products of dimethylamine that was used in its $ZNCl_2$ process (see pages 167-168 and 191 of Peng Dong's deposition dated March 29, 2021), products that could include nitrosamines such as NDMA. The issue of foreseeability of the formation of nitrosamine impurities with use of both the TEA process and the $ZNCl_2$ process for valsartan synthesis has been addressed by Dr. Hecht, an expert in organic chemistry in this case. In his report, he states that *"the introduction of NDMA and NDEA into ZHP's Valsartan API was easily foreseeable"* (see page 18 of 123 Dr. Hecht's expert report dated July 6, 2021). Yet, it was ZHP's responsibility to ensure the quality of its valsartan as part of its obligations under cGMP regulations. By not conducting a full risk assessment related to nitrosamine decomposition products formed during the TEA and the $ZNCl_2$ processes, ZHP put patient health at risk. My opinion about putting patient health at risk is supported by FDA statements on this issue:

> *"We're continuing to investigate and take action to protect patient health and safety from products in this angiotensin II receptor blocker class that have been found to have dangerous impurities. As part of that investigation, we've uncovered serious manufacturing violations at ZHP, which is one of the manufacturing facilities that has been linked to these products. The issues cited in the warning letter are associated with*

the nitrosamine impurities found in these drugs, and these violations reveal a disturbing lack of oversight at this API manufacturer that puts patients at risk."[40]

47. Evidence in the case also shows that in July of 2017, ZHP employees were discussing internally the issue of sartan[41] impurities resulting from their processes, including NDMA in ZHP's valsartan – stating, *"the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic."* (ZHP00190573).[42] In this July 27, 2017 email, Jinsheng Lin (responsible for the research laboratory around the valsartan process) also expressed the following about nitroso compounds in their sartan APIs:

> *"If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be an* ***extremely high GMP risk****. This is a common problem with the production and synthesis of sartan APIs. It is* ***recommended to improve other quenching processes (such as NaClO) along with the optimization of the valsartan sodium azide quenching process.***
>
> *I've also attached a patent from a 2013 sodium azide NAClO quenching method by Zhejiang Second Pharma Co., Ltd. They proposed that the use of NaNO2 quenching will result in the formation of N-NO impurities. At the same time, they used ZHP's crude valsartan in their LC-MS test and detected this impurity. This indicates that* ***other companies have paid attention to the quality problem very early on****. So leaders please pay attention to this issue." [emphasis added]*

This evidence shows that ZHP understood at least by 2017 that nitrosamines were created in the production generally of ZHP's sartan APIs, including NDMA in valsartan (see deposition of Dr.

[40] FDA press release at https://www.fda.gov/news-events/press-announcements/fda-warns-api-manufacturer-involved-valsartan-recall-provides-information-patients-taking-these.
[41] The term "sartan" is used to identify a class of angiotensin II receptor blocking drugs that included valsartan.
[42] Eric Gu of ZHP testified, "You have to update the impurity profiles once you gain more and more knowledge, right. And I know the impurity profile, CoA is always being updated as we discover more and more, as the science rises, okay. (see deposition of Eric Gu at page 331). ZHP should have updated its valsartan impurity profile to include NDMA and notified the FDA prior to 2018.

Min Li at pages 82-92 of his deposition dated April 20, 2021).[43] ZHP should have removed its valsartan from the market at this time, as Dr. Eric Gu testified, *"If we knew, okay, there's NDMA in valsartan, you know, ZHP wouldn't sell that. That's why it's also – as soon as we learn there are NDMA in the valsartan, ZHP recall all the products form the market."* (see pages 391-392 of Eric Gu's deposition dated April 6, 2021).

48. Dr. Li (who was on the July 27, 2017, email acknowledging NDMA in ZHP's valsartan) also confirmed that ZHP had received complaints from customers beginning in 2014 of unknown peaks identified through chromatography that ZHP failed to investigate (see pages 261-265 of Dr. Li's deposition).[44] Dr. Li acknowledged that it was ZHP's responsibility to ensure quality of its valsartan products (see page 268 of Dr. Li's deposition). Yet, it was one of ZHP's customer's, not ZHP, that identified NDMA as an impurity in the valsartan it purchased from ZHP (Prinston00075797 at 5803). Thus, evidence shows that the failure of ZHP to ensure the quality of its valsartan products was an ongoing issue as far back as 2014. These problems were recognized by FDA in a November 29, 2018, Warning Letter[45] that followed FDA inspections of ZHP in July and August of 2018.

49. With respect to the presence of nitrosamine impurities in ZHP's valsartan drug products, Dr. Li also confirmed that every batch of valsartan produced using ZHP's zinc chloride process exceeded a reasonably safe daily intake level set by FDA of 96 nanograms per day (see page 306 of Dr. Li's deposition of April 21, 2021). It is important to note that in 2019 the FDA determined that there is no acceptable specification for nitrosamines in valsartan (TORRENT-MDL2875-00215093; TEVA-MDL2875-00154437; ZHP00116661):

> *"Due to their known potent carcinogenic effects, and because it is feasible to limit these impurities by taking reasonable steps to prevent or eliminate their presence,* ***FDA has determined that there is no acceptable specification for nitrosamines in ARB API***

[43] This at odds with a December 20, 2018 email from Wayne Cheng (ZHP Quality Management Dept) to Min Li claiming, "*We regret but recognized that the possibility of formation of NDMA based on the chemistry involved in the manufacturing Valsartan API was not foreseen due to the lack of the experience, and not fully understand the mechanistic chemistry at time in 2011, plus the failure to conduct thorough risk-based evaluation on possible impurity profiles is also a major factor from the first place, which together resulted in failure to identify the potential to generate NDMA in valsartan API by process change."* (ZHP00406066).
[44] See paragraph 32 – it is the responsibility of the manufacturer to detect and identify unknown impurities.
[45] PRINSTONO0077339.

[angiotensin receptor blocker active pharmaceutical ingredients] and DP [Drug Product]. Therefore, FDA advises that nitrosamines should be absent (i.e., not detectable as described below) from ARB API and ARB drug products*." [emphasis added]*

*****

"In addition, DP manufacturers should test each API lot received from each supplier before releasing the API for use until the DP manufacturer has verified that the supplier can consistently produce API without a detectable nitrosamine."

*****

"API batches may be reprocessed, reworked, and/or reconditioned to be rendered absent of a detectable nitrosamine impurity as provided for in existing policies for amending or supplementing and controlling such operations."

*****

"Batch testing to verify no detectable nitrosamine in the API should continue unless the API producer has demonstrated their process is not at risk for producing detectable nitrosamine in accordance with guidance (see, e.g., ICH Q7). This includes demonstrating that:

- *starting materials, including vendor-supplied intermediates, have no detectable nitrosamines or such amounts can be purged such that the API contains no detectable amounts of nitrosamines, and*
- *raw materials used in the process, including recovered solvents and catalysts, contain no detectable amounts nitrosamines."*

In 2020 the FDA stated, *"when feasible, manufacturers of API and drug products should take reasonable steps to prevent or eliminate N-nitrosamines."* (ZHP00243853). Moreover, as discussed by Dr. Hecht in his report, it is feasible to prevent the formation of NDMA and NDEA in valsartan because chemical processes exist to make valsartan that do not produce NDMA or NDEA impurities.

50. Finally, it is important to note that evidence existed in the scientific literature before 2010 that NDMA could be formed from the reaction of dimethylamine and nitrous acid, the chemical reaction that could occur in valsartan's zinc chloride process (Min Li Exhibit ZHP-

311; Peng Dong Exhibit ZHP-197; IARC monograph 1978). ZHP was apparently unaware of this literature. Based on my experience and training, research of the scientific literature would be an appropriate first step when chemical process changes are being considered. If ZHP would have performed an adequate risk assessment on the changes to their valsartan synthesis process, they would have been aware that their valsartan process had the potential to form NDMA.

51. Once FDA was made aware of an issue of nitrosamine impurities in valsartan in 2018, the agency did begin to act. The FDA website[46] contains a listing of actions the agency has taken since July of 2018 with respect to nitrosamine impurities in not only valsartan, but also a variety of other marketed drugs.

52. Considered together, evidence in this case shows that Defendants made human drug products that posed a risk to patients based on the presence of nitrosamines such as NDMA and NDEA in their valsartan API and/or finished drug products. Yet, neither ZHP or any of the other ANDA holders performed the necessary risk assessment for degradation products from ZHP's valsartan processes; such risk assessment activities, if adequately performed, should have led to identification of the potential and actual presence of nitrosamine impurities in ZHP's valsartan products. The presence of the potent genotoxic impurities in ZHP's valsartan products unnecessarily put patient health at risk.

VII. Valsartan Manufacturers Are Responsible for Ensuring that Their Drug Products Are Safe for Human Use

53. Although FDA plays an important role in protecting public health through enforcement of applicable laws and regulations, as already discussed above, it is the ANDA holders that are ultimately are responsible for ensuring the quality of marketed APIs and finished drug products and providing physicians and their patients with products that are both effective and safe.

[46] https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications#:~:text=FDA%20has%20been%20investigating%20the,to%20some%20level%20of%20nitrosamines.

54. In this case, there is one manufacturer, ZHP, that supplied three other companies (Prinston[47], Teva, and Torrent) with either the valsartan API or finished dose forms of valsartan. ZHP was the only company in this case that was both an API and a finished dose form valsartan manufacturer; ZHP was owner of the valsartan Drug Master File that related to the production of valsartan with nitrosamine impurities (DMF 023491) and their US agent for the Drug Master File was Huahai US. The DMF specifically notes the following (HUAHAI-US00007752 at 7899-7901; PRINSTON00080011 at 0119-0121):

> *"The impurity ABC are listed in the monograph of Valsartan from USP, all the limits of these impurities comply with Pharmacopeia. Hence, these impurities are considered with corresponding toxicological information and* ***no genotoxic risk in Valsartan****.*
>
> *Regarding of the impurity D-J and hydrolysis product****, there is not any high potency genotoxic group, such as****, aflatoxin-like-,* ***N-nitroso-****, and azoxy-compound has been included in these impurities."*
>
> *****
>
> *For the materials used in the manufacturing process and not discussed in quality analysis for Valsartan, the information available of risk and safety (R phrases) out of safety data sheets are listed below. Moreover, they are highly reactive compounds which could be reacted and decomposed during the synthesis and work-up.* ***No genotoxic potential is associated with these materials and these materials do not have to be further specified and/or controlled with respect to the genotoxicity risk evaluation****." [emphasis added]*

The valsartan that ZHP manufactured containing NDMA or NDEA did not comply with the specifications within its Drug Master File. Prinston (US ANDA 204821; US ANDA 206083), Teva Pharmaceutical Industries Ltd[48] (US ANDA 090642; US ANDA 077530; US ANDA 091235; US Anda 091519; US ANDA 200435) and Torrent (US ANDA 202728; US ANDA 202377) held ANDA's of their own based on use of ZHP's valsartan API and/or finished dose forms. None of the valsartan ANDAs or supplements disclosed NDMA or NDEA as an impurity (see e.g., ZHP01451842; PRINBURY00058083; PRINSTON00037968; PRINSTON00177677;

[47] Prinston subsidiary, Solco, marketed Prinston's finished dose forms of valsartan that were manufactured by ZHP in China.

[48] It should be noted that Watson Labs Inc. and Ohm Labs Inc. may be listed as ANDA holders but those companies and their ANDA's are owned by Teva.

PRINSTON00183155; PRINBURY00058078; TEVAL-MDL2875-00001789; TEVA-MDL2875-00279311; TEVA-MDL2875-00950663; TORRENT-MDL2875-00003946; TORRENT-MDL2875-00000736). The valsartan finished doses that contained NDMA or NDEA did not comply with the specifications with the ANDAs.

55. ZHP's quality agreements showed that various ZHP partners shared responsibilities for the products produced (*e.g.,* PRINSTON00463638; PRINSTON00463676; TEVA-MDL2875-00020279; TEVA-MDL2875-00020212; TEVA-MDL2875-00020213; TEVA-MDL2875-00020214; TORRENT-MDL2875-00536415; TORRENT-MDL2875-00291332). Considering the relationships among the various companies in this case, the Defendants collectively were responsible for ensuring that the product being marketed and sold in the US was both effective and safe. A key issue in drug safety, as already mentioned above, is ensuring that products are manufactured in compliance with FDA cGMPs and do not contain any impurities. Compliance with cGMPs is the responsibility of the drug manufacturer (both API and finished dose), not the FDA. Torrent sent the following to ZHP in a document titled "Notice for Payment of Damages /Compensation under the Technical and Quality Agreements" on February 13, 2019 (ZHP02592303):

> *"Needless to state that purchase of the API by Torrent from Huahai was premised on the basis of various representations and warranties furnished by Huahai as regards the quality and safety of the API. In terms of the TQAs, Huahai had at all times provided to Torrent certificates certifying the quality aspects of the API and regulatory compliances in respect of the API. Significantly, amongst other representations, Huahai had repeatedly provided to Torrent declarations regarding genotoxic impurities, declaring that the API did not have any genotoxic impurities or that such impurities were within the prescribed acceptable limits. Further, Huahai had made express stipulations in respect of regulatory and pharmacopeial compliance on its part and warranted that it was compliant with all prevailing laws and regulations inter alia pertaining to health and safety of the API. Significantly, it was also expressly warranted by Huahai that it would be held fully liable with respect to any claim (whether from private parties or public bodies) which may arise due to Huahai failing to meet the applicable laws, regulations and generally expected standards."*

*****

> *"it is now clear that contrary to Huahai's declarations regarding the absence of genotoxic impurities, the API supplied by Huahai to Torrent did contain certain genotoxic impurities, namely, N-Nitroso-dimethylamine ("NDMA") and N-Nitrosodiethylamine ("NDEA") on account of the manufacturing process employed by Huahai and thus there has been a clear breach of the representations and warranties provided by Huahai to Torrent. It is also clear that these impurities were present in all batches of the API supplied by Huahai. Since NDMA and NDEA have been classified as a probable human carcinogenic, Torrent had to recall all its existing batches of formulations containing Valsartan from the various jurisdictions, including, United States and stop any further sale."*

Teva sent similar correspondence to ZHP regarding nitrosamine impurities in their valsartan API (TEVA-MDL2875-00324735; TEVA-MDL2875-00614800). While ZHP did not comply with its quality agreements, it is still the finished dose manufacturer's responsibility to ensure that the API they are purchasing and the finished dose they are selling do not contain harmful impurities. Quality agreements do not absolve finished dose manufacturers from their responsibilities regarding drug quality.

56. Like all areas within the FDA, in generic drug postmarket compliance, as well as issues of foreign manufacturing, FDA is underfunded and understaffed (GAO, 2022; GAO, 2020; GAO, 2010; IOM, 2007). As discussed in a recent report by the Government Accounting Office (GAO, 2022) entitled *Drug Safety: FDA Should Take Additional Steps to Improve Its Foreign Inspection Program*:

> *"While drugs manufactured overseas for the U.S. market must meet the same requirements as those manufactured in the U.S., these unique challenges raise questions about the equivalence of foreign to domestic inspections. FDA plans on implementing pilot programs focused on evaluating the effect of conducting unannounced inspections and using independent translation services."*

Also acknowledged in the 2022 report is the fact that FDA has had a long-standing problem with understaffing in the inspection programs (GAO, 2022; GAO, 2020; GAO, 2016; GAO, 2011; GAO, 2010; GAO, 2008). These limitations in terms of FDA resources in areas that impact the

safety of generic drug products are important to consider, even though the ultimate responsibility for ensuring safety of a drug product always rests on the application holder, not the FDA, particularly after the drug product enters the marketplace. These FDA limitations provide context for why it is so important for companies to be vigilant about compliance with quality standards and fully complying with cGMPs. It also is important to remember that there are over 20,000 prescription drug products for which FDA has oversight,[49] as well as thousands of other therapeutic products (OTC drugs, medical devices, *etc*.). This is one reason why it is so important for individual NDA and ANDA holders to fully comply with cGMP regulations; FDA does not have the staff to ensure that each batch of drug product manufactured is in compliance with applicable regulations.

57. In terms of ensuring that drug products sold are safe for use as directed, manufacturers have tools available to them that could allow them to directly inform physicians and their patients about safety concerns. These tools include Dear Healthcare Provider letters (discussed above in paragraph 39) and even withdrawal of a product from the market if the safety concern is significant enough to warrant such action. In this case, there is no evidence to show that any of the ANDA holders took actions on their own to warn physicians and their patients about the presence of impurities in valsartan drug products that were carcinogens. The lack of timely information on the presence of probable human carcinogens as impurities in various valsartan products put patient health at risk.

VIII. Valsartan Drug Manufacturers Are Responsible for Monitoring Their Manufacturing Process, Including Changes to Their Manufacturing Process, To Ensure that Impurity and Contaminant Profiles Do Not Change Over Time

58. One of the companies that considered using ZHP's API in the manufacture of their valsartan finished drug products was Novartis. It was Novartis that notified ZHP in 2018 (May) of a quality issue with valsartan based on their own checking of the API provided to them

[49] https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance#:~:text=There%20are%20over%2020%2C000%20prescription,621%20FDA%2Dlicensed%20biologics%20products.

by ZHP (ZHP00389304).[50] Based on my training and experience, this is what a responsible drug manufacturer would do. As mentioned above, other ZHP customers had contacted the company as far back as 2014 questioning the presence of impurities in ZHP's valsartan products. Yet, ZHP claims no investigation was undertaken until 2018 to specifically identify the impurities in valsartan as potent genotoxic agents such as NDMA and NDEA. The delay in investigation of the presence of drug impurities before 2018 put patient health at risk and is inconsistent with compliance with cGMP regulations in the US as well as ICH standards.

59. The responsibility of drug manufacturers is confirmed when the FDA's 2018 Warning Letter to ZHP is reviewed (ZHP01344159). As stated by FDA (see page 1):

> *"[b]ecause your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B)."*

The letter gives a detailed explanation of the lack of cGMP compliance by ZHP as it related to valsartan API as well as another drug API (levetiracetam). FDA mentions that the issues with impurities in valsartan related to both the TEA process and the $ZNCl_2$ process. The FDA informed ZHP as well that FDA's analyses of samples *"identified amounts of NDMA in valsartan API manufactured at your firm".* The serious nature of FDA's findings is conveyed in the letter when they stated: *"FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation."*

60. Considered together, evidence in this case shows that when a company fails to fulfill its duties under the FDA regulations and other industry standards, patient health is put at risk. In this case, due to a lack of compliance with cGMPs, patients have been exposed to impurities that have been identified as potent genotoxic agents and *in vivo* carcinogens which is an important issue for patient safety.

[50] Prinston then notified the FDA of the presence of NDMA in their valsartan on June 18, 2018. (PRINSTON00000001).

IX. Valsartan Drug Products and FDA Standards

61. Since valsartan generic drug products are asserted to be pharmaceutical equivalents of Diovan, the RLD at issue in this case, the presence of nitrosamine impurities is important. The valsartan USP monograph, which is based off the impurity profile of Diovan, does not list NDMA or NDEA as acceptable impurities. Additionally, the valsartan molecule does not breakdown into NDMA or NDEA. Furthermore, testing of Diovan has demonstrated that it can be manufactured without any nitrosamine impurities (see analysis by Health Canada of Diovan samples at page 9 of 17[51]). Therefore, the presence of NDMA or NDEA in valsartan is unacceptable, as it renders the drug product not therapeutically/ pharmaceutically equivalent to the RLD approved by the FDA. As discussed in some detail above, drug products are therapeutically equivalent to a RLD (Diovan is the RLD) if they are pharmaceutical equivalents. By virtue of the difference in purity of valsartan with NDMA or NDEA and Diovan, the generic valsartan products that were linked to ZHP's manufacturing were not pharmaceutical equivalents.

62. Evidence in this case clearly demonstrates that valsartan API and finished drug products manufactured and marketed by Defendants were "adulterated" due to the presence of nitrosamine impurities. Consistent with FDA's definition of an "impurity", as well as the definitions of other relevant authorities (USP, ICH), nitrosamines such as NDMA and NDEA in valsartan API's and finished drug products are impurities. Then, as discussed earlier in this report in paragraph 25:

> *"A drug or device shall be deemed to be* ***adulterated*** *(351) (a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture (1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or (2)(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health;* ***or (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets***

[51] https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/angiotensin-receptor-blocker.html.

the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess*; …" [emphasis added]*

Thus, the lack of conformity with cGMPs and the presence of nitrosamines in valsartan API and finished drug products rendered valsartan drug products adulterated as defined in FDA laws and regulations.

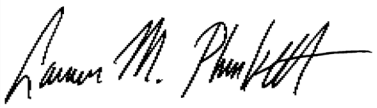
63. Even more important than the fact that the valsartan drug products sold in the US were adulterated is the fact that the nitrosamine impurities in valsartan drug products put patient health at risk. As a toxicologist and regulatory expert, the presence of impurities in drugs used chronically to treat health conditions that are probable human carcinogens (*i.e.,* NDMA and NDEA) is a clear patient safety concern.

X. Additional Information

64. I reserve the right to supplement my opinions in this case if additional evidence related to those opinions becomes available after the deadline for filing of this report.

XI. Compensation

65. My compensation in this matter is at the rate of $400.00 per hour.



Laura M. Plunkett, Ph.D., DABT

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APPENDIX A

Curriculum Vitae

CURRICULUM VITAE

Laura M. Plunkett, Ph.D., D.A.B.T

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Houston, TX 77077

EDUCATION

1984	Ph.D.	Pharmacology	University of Georgia
1980	B.S.	Zoology	University of Georgia

PROFESSIONAL EXPERIENCE

Registered Patent Agent Licata & Tyrrell, P.C., Marlton, N.J., 1999 – present
Assists clients with obtaining patent protection, specializing in products used in medical applications (drugs, devices, dietary supplements). Assists clients with developing regulatory strategies for commercialization of their inventions. Provides regulatory support for companies engaged in manufacturing and marketing of products regulated by the U.S. Food and Drug Administration, the U.S. Environmental Protection Agency and other regulatory bodies in the U.S. and worldwide.

Partner. BioPolicy Solutions LLC, June 2020 – present
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

President. Integrative Biostrategies (IB) LLC, 2001- May 2020
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

Owner. Plunkett & Associates, Houston, Texas, 1997 – 2001
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and

Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Houston, Texas, 1992 – 1997

Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Arlington, Virginia, 1989 – 1992

Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug administration.

Assistant Professor. University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, 1986 – 1989

Taught medical and graduate student courses in pharmacology (lecture and laboratory), neurosciences, cardiovascular pharmacology, and neuropharmacology. Performed basic research in area of autonomic control of cardiovascular function and neurochemical systems involved in autonomic function. Recipient of extramural funding from the Arkansas Heart Association (principal investigator).

Postdoctoral fellow. National Institute of General Medical Sciences, Pharmacology Research Associate Training Program, 1984 – 1986

Performed basic research in area of neurochemical control of cardiovascular function and neurochemical systems involved in autonomic function.

Research Assistant. University of Georgia, College of Pharmacy, Department of Pharmacology and Toxicology 1980 – 1984

Taught laboratory courses in pharmacology to pharmacy students as part of graduate student assistantship responsibilities.

HONORS AND AWARDS

Chosen for PRAT program at National Institutes of Health. Pharmacology Research Associate Training Program, 1984-1986.

Rho Chi. The University of Georgia, College of Pharmacy, Initiated, 1984.

Recipient of Excellence in Graduate Research Award. The University of Georgia, College of Pharmacy, 1983.

Alpha Lambda Delta. The University of Georgia Chapter, 1978.

PROFESSIONAL CERTIFICATION

Registered patent agent, 1999 [Registration No. 45,015]
Diplomate, American Board of Toxicology, 1993 to present.

ACADEMIC AFFILIATION

Adjunct Professor. Baylor University, Department of Environmental Science, 2017-present

PROFESSIONAL MEMBERSHIPS

Member, Society of Toxicology 1992 – present

President, Society of Toxicology Risk Assessment Specialty Section (RASS) 2021-2022

Vice-President, Society of Toxicology Risk Assessment Specialty Section (RASS) 2020-2021

Vice-President Elect, Society of Toxicology Risk Assessment Specialty Section (RASS) 2019-2020

Member, Lone Star Chapter Society of Toxicology 2007 – present

Councilor, Lone Star Chapter Society of Toxicology 2010 - 2013

Secretary, Lone Star Chapter Society of Toxicology 2013 – 2015

Vice President, Lone Star Chapter Society of Toxicology 2015-2016

President, Lone Star Chapter, Society of Toxicology 2016-2017

Past President, Lone Star Chapter, Society of Toxicology 2017-2018

Member, American College of Toxicology, 1997 - present

Member, Society for Risk Analysis, 2007- present

President, Lone Star Chapter of the Society for Risk Analysis, 1998

Councilor, Lone Star Chapter of the Society for Risk Analysis, 1999-2000

Member, Regulatory Affairs Professionals Society, 2003 - present

Member, Society for Neuroscience 1985 - present

Member, American Association for Pharmaceutical Sciences 1992 – present

Member, Society for Environmental Geochemistry and Health 1992 - present

Member, ASTM Committee E06, 1990 – present

Member, International Association of Plumbing and Mechanical Officials (IAPMO) Committee Z1123 (Prop 65) Committee, 2020 - present

PUBLICATIONS

1. Bobst, S, Ryan, K, **Plunkett, LM,** Willett, KL. 2020. ToxPoint: Toxicology studies on Δ9-tetrahydrocannabinol and cannabidiol-containing products available to consumers are lacking. *Toxicol. Sci.* 178:1-2.

2. Rajendran, N, Seagrave, JC, **Plunkett, LM**, MacGregor, JA. A comparative assessment of the acute inhalation toxicity of vanadium compounds. *Inhal. Toxicol.* 2016. 28:618-628.

3. Cox, LA, Popken, DA, Kaplan, AM, **Plunkett, LM**, Becker, RA. How well can in vitro data predict in vivo effects of chemicals? Rodent carcinogenicity as a case study. *Regul. Toxicol. Pharmacol.* 2016. 77:54-64.

4. **Plunkett, LM**, Kaplan, AM, Becker, RA. Challenges in using the ToxRefDB as a resource for toxicity modeling. *Regul. Toxicol Pharmacol*. 2015. 72:610-614.

5. **Plunkett, LM**, Becker, RA, Kaplan, M. An enhanced tiered toxicity testing framework with triggers for assessing hazards and risks of commodity chemicals. *Regul. Toxicol. Pharmacol*. 2010. 58:382-394.

6. Chambers, A, Krewski, D, Birkett, N, **Plunkett, L,** Hertzberg, R, Danzeisen, R, Aggett, PJ, Starr, TB , Baker, S, Dourson, M, Jones, P, Keen, CL , Meek, B, Schoeny, R, and Slob, W *J.* An exposure-response curve for copper excess and deficiency. *Toxicol. Environ. Health.* 2010. 13:546- 578.

7. Krewski, D, Chambers, A, Stern, BA, Aggett, PA, **Plunkett, L,** Rudenko, L. Development of a copper database for exposure-response analysis. *J. Toxicol. Environ. Health.* 2010. 73:208-216.

8. **Plunkett, LM**, Becker, RA. Does the standard toxicological testing paradigm for industrial chemicals apply to screening for children's health risks? *The Open Toxicol. J.* 2008, 2:42-60.

9. Becker, RA, **Plunkett, LM**, Borzelleca, JF, Kaplan, AM. Tiered toxicity testing: Evaluation of toxicity-based decision triggers for human health hazard characterization. *Food Chem. Toxicol*. 2007, 45:2454-2469.

10. MacGregor, JA, **Plunkett, LM**, Youngren, SH, Manley, A, Plunkett, JB, Starr, TB. Humans Appear No More Sensitive than Laboratory Animals to the Inhibition of Red Blood Cell Cholinesterase by Dichlorvos (DDVP). *Regul. Toxicol. Pharmacol*., 2005, 43:150-167.

11. **Plunkett, LM.** Do current FIFRA guideline tests protect infants and children? Lead as a case study. *J Regul Toxicol Pharmacol* 1999;29:80-87.

12. **Plunkett, LM,** Seifen E, Kennedy RH. Effect of morphine pretreatment on cocaine cardiotoxicity in anesthetized guinea pigs. *Arch Int Pharmacodyn* 1989;297:60-67.

13. Zorbas M., Owens SM, **Plunkett LM,** Bui H. The pharmacokinetics of [3H]-[1-(2-thienyl)cyclohexyl]piperidine (TCP) in Sprague Dawley rats. *J Drug Metab Disposit* 1989;17:641-645.

14. Seifen E, **Plunkett LM,** Kennedy RH. Cardiovascular and lethal effects of cocaine in anesthetized dogs and guinea pigs. *Arch Int Pharmacodyn* 1989;300:241-253.

15. McCarty R, **Plunkett LM.** Regulation of binding sites for atrial natriuretic factor (ANF) in rat brain. *Peptides* 1988;9(S1):3-8.

16. Stewart RE, Swithers SE, **Plunkett LM,** McCarty R. ANF receptors: distribution and regulation in central and peripheral tissues. *Neurosci Biobehav Rev* 1988;12:151-168.

17. **Plunkett LM,** Tackett RL. Central dopamine receptors and their role in digoxin-induced cardiotoxicity in the dog. *J Pharm Pharmacol* 1987;39:29-34.

18. **Plunkett LM,** Tackett RL. Increases in CSF norepinephrine associated with the onset of cardiac glycoside toxicity. *Eur J Pharmacol* 1987;136:119-122.

19. McCarty R, **Plunkett LM.** Quantitative autoradiographic analysis of somatostatin binding sites in discrete areas of rat brain. *Brain Res Bull* 1987;18:289-94.

20. **Plunkett LM,** Shigematsu K, Kurihara M, Saavedra JM. Localization of angiotensin II receptors along the anteroventral-third ventricle area of the rat brain. *Brain Res* 1987;405:205-212.

21. Israel A, **Plunkett LM,** Saavedra JM. Increased number of angiotensin II binding sites determined by autoradiography in anterior pituitary of water deprived and Brattleboro rats. *Neuroendocrinol* 1986;42:57-63.

22. Saavedra JM, Correa FMA, **Plunkett LM,** Israel A, Kurihara M, Shigematsu K. Angiotensin and atrial natriuretic peptide binding in brain of hypertensive rats. *Nature* 1986;320:758-760.

23. McCarty RM, **Plunkett LM.** Forebrain atriopeptin binding sites: Alterations in spontaneously hypertensive rats. *Neurochem Int* 1986;9:177-183.

24. Shigematsu K, Saavedra JM, **Plunkett LM,** Kurihara M, Correa FMA. Angiotensin II binding sites in the anteroventral-third-ventricle (AV3V) area and related structures of the rat brain. *Neurosci Lett* 1986 67:37-41.

25. Correa FMA, **Plunkett LM,** Saavedra JM. Quantitative distribution of angiotensin-converting enzyme (kininase II) in discrete areas of the rat brain by autoradiography with computerized microdensitometry. *Brain Res* 1986;275:259-266.

26. Saavedra JM, Israel A, **Plunkett LM,** Kurihara M, Shigematsu K, Correa FMA. Quantitative distribution of angiotensin II binding sites in rat brain by autoradiography. Peptides 1986;7:679-687.

27. McCarty R, **Plunkett LM**. Binding sites for atrial natriuretic factor (ANF) in brain: alterations in Brattleboro rats. *Brain Res Bull* 1986;17:767-772.

28. **Plunkett LM,** Gokhale RD, Vallner JJ, Tackett RL. Prazosin alters free and total plasma digoxin in dogs. *Am Heart J* 1985;109:847-851.

29. **Plunkett LM,** Tackett RL. The effects of central beta-receptor antagonism on digoxin cardiotoxicity. *Res Comm Chem Path Pharmacol* 1985;48:209-220.

30. Israel A, Saavedra JM, **Plunkett L.** Water deprivation upregulates angiotensin II receptors in rat anterior pituitary. *Am J Physiol* 1985;248 (Endocrino. Metabl.

II):E264-E267.

31. Niwa M, Shigematsu K**, Plunkett L,** Saavedra JM. High affinity substance P binding sites in rat sympathetic ganglia. *Am J Physiol* 1985;249 (Heart Circ. Physiol 18):H694-H697.

32. Correa FMA, **Plunkett LM,** Saavedra JM, Hichens M. Quantitative autoradiographic determination of angiotensin-converting enzyme (kininase II) kinetics in individual rat brain nuclei with 125I-351A, a specific enzyme inhibitor. *Brain Res* 1985;347:192-195.

33. Israel A, Niwa M, **Plunkett LM,** Saavedra JM. High affinity angiotensin receptors in rat adrenal medulla. *Regul Pept* 1985;11:237-243.

34. Israel A, **Plunkett LM,** Saavedra JM. Quantitative autoradiographic characterization of receptors for angiotensin II and other neuropeptides in individual brain nuclei and peripheral tissues from single rats. *Cell Mol Neurobiol* 1985;5:211-222.

35. **Plunkett LM,** Correa FMA, Saavedra JM. Quantitative autoradiographic determination of angiotensin-converting enzyme kinetics in rat pituitary and adrenal glands with 125I-135A, a specific inhibitor. Regul Pept 1985;12:1-10.

36. **Plunkett LM,** Saavedra JM. Increased angiotensin II binding affinity in the nucleus tractus solitarius of spontaneously hypertensive rats. *Proc Natl Acad Sci* 1985;82:7721-7724.

37. **Plunkett LM,** Tackett RL. Central alpha receptors and their role in digoxin cardiotoxicity. *J Pharmacol Exp Ther* 1983;227:683-686.

ABSTRACTS

1. **Plunkett, L.M.** Cannabidiol Incorporation into Consumer Products in the US: Regulatory Challenges to Commercialization. Presenting at the Society of Toxicology annual meeting. March 25, 2021. Virtual Meeting.

2. **Plunkett, LM**. Cannabidiol Incorporation into Consumer Products in the US: Regulatory Challenges to Commercialization. Presenting at the annual meeting of the American Association for the Advancement of Science (AAAS), February 8-11, 2021. Virtual meeting

3. **Plunkett, LM**. Marijuana and Public Safety Concerns: States in Charge. Presenting at

Society of Toxicology annual meeting. March 11-15, 2018, San Antonio, Texas.

4. Cox, LA, Popken, DA, Kaplan, AM, **Plunkett, LM**, Becker, RA. How well do High Throughput Screening (HTS) assay data predict in vivo rodent carcinogenicity of pesticides? Presenting at Society for Risk Analysis annual meeting, December 11-15, 2016, San Diego, California.

5. **Plunkett, LM**. THC and legal issues related to the state of the science. Symposium presenter at the Society of Toxicology, New Orleans, LA, March 2016.

6. Goyak, K, Alyea, R, Becker, RA, **Plunkett, LM**, Plunkett, JB. Evaluating the ability of high-throughput screening (HTS) assays to capture the biological activity of industrial chemicals. Poster presentation at the Society of Toxicology, New Orleans, LA, March 2016.

7. MacGregor, JA, Plunkett, JB, **Plunkett, LM.** The occurrence of chemically induced lung tumors in rodents as an outcome in NTP chronic bioassays and the impact on cancer classifications. Presented at the Society of Toxicology, San Diego, CA, March 2015.

8. Urban, JD, Thompson, CM, **Plunkett, LM**, Perry, C, Haws, LC. A state of the science of copper reference dose for soil remediation. Presented at the Society of Toxicology, San Diego, CA, March 2015.

9. **Plunkett, LM**, Kaplan, AM, Becker, RA. Evaluation of a tiered toxicity testing decision trigger for assessing reproductive hazards of commodity chemicals. Submitted for presentation at the Society of Toxicology, Phoenix, AZ, March 2014.

10. **Plunkett, L.M.** Overview of key public and worker health concerns in Texas food production. Presented at the Society of Toxicology, San Antonio, TX, March 2012.

11. **Plunkett, L.M.**, Starr, T.B., MacGregor, J.A., Manley, A. Corn oil as a causative factor for proliferative lesions of the forestaomach in B6C3F1 mice exposed by gavage. Presented at Society of Toxicology, Washington, D.C., March 9, 2011. [Award received for "Best Presentation"]

12. **Plunkett, LM**, MacGregor, JA, Starr, TB, Manley, A. Daily gavage with corn oil is a causative factor for proliferative lesions of the forestaomach in B6C3F1 mice. Toxicology Lett. 189S:S142. Presented at EUROTOX, Dresden, Germany, September 14, 2009.

13. **Plunkett, LM**, MacGregor, JA, Starr, TB, Youngren, SH, Manley, A. Determination of a dichlorvos-specific acute interspecies uncertainty factor. Society of Toxicology, Seattle, WA, March 19, 2008.

14. **Plunkett, LM**, Starr, TB, Youngren, SH, MacGregor, JA, Manley, A. Determination of the magnitude of intraspecies differences in red blood cell cholinesterase inhibition in response to dichlorvos exposure. Society of Toxicology, San Diego, CA, March 6, 2006.

15. **Plunkett, LM**, Licata, JM. What every technology manager needs to know about FDA law. Association of University Technology Managers (AUTM), Orlando, FL, March 4, 2006.

16. **Plunkett, LM,** Licata JM. What every technology manager needs to know about FDA law. Association of University Technology Managers (AUTM), Phoenix, AZ February 2005.

17. **Plunkett, LM**. Qualitative Interpretation of Complex and Disparate Data Sets for Dose-Response Assessment of Essential Trace Elements: Copper as a Case Study. Society for Toxicology, Baltimore, MD March 2004 .

18. **Plunkett, LM.** Evaluating qualitative and quantitative dose-response data in complete data sets for comparative dose-response assessment. Soc. Risk Analysis, Baltimore, MD, December 10, 2003.

19. **Plunkett, LM**, Rieth S, Starr T. Issues in assessing risks for cholinesterase-inhibiting pesticides: A decision tree approach. Soc. Risk Analysis, New Orleans, LA, December 9-12, 1996

20. **Plunkett, LM**, Brown S. Assessment of the potential neuropathic risk to banana workers from dermal exposure to chlorpyrifos. Soc. Risk Analysis, Honolulu, HI, December 3-7, 1995

21. **Plunkett, LM**, Russell K. Cooperation versus Confrontation: Reconciling Lead regulations, exposure studies, and public perception. SEGH Conference, July, Salt Lake City, UT, 1994

22. **Plunkett LM**, Wixtrom RN, Cabrera CR. Evaluation of the long-term safety of inflatable penile prostheses: a critical analysis of potential carcinogenic, reproductive, teratogenic, or adverse immunological effects of silicone. Western Section of American Urological Association Meeting, Seattle, WA, August 21-25, 1994

23. Wixtrom RN, **Plunkett LM**, Clarkin CM. Complications of inflatable penile prostheses: A comprehensive review of infection, mechanical complications, erosion/migration/extrusion, and fibrous capsule formation. 1994.

24. Wixtrom RN, Clarkin CM, Purkait B, **Plunkett LM**. A review of clinical experience with the Mentor Alpha I and Mark II inflatable penile prostheses. 1994.

25. **Plunkett LM**, Rosolowsky LJ, Lerner DM, Washburn ST. A biokinetic model for predicting blood lead levels in adults living near a former battery recycling facility. SEGH Conference, New Orleans, LA, July, 1993.

26. Rosolowsky LJ, Edelmann KG, **Plunkett LM**. A biokinetic model for predicting blood lead levels in adults that accounts for intermittent exposures. Society for Risk Analysis, December, 1993

27. **Plunkett LM**, Owens SM , Gunnell M, Owens RB. The effect of chronic phencyclidine (PCP) and phenylcyclohexene (PC) dosing on [3H]TCP and [3H] haloperidol binding in rat brain. *FASEB J* 1990;4:A329.

28. Owens RB, Owens SM, Gunnell M, **Plunkett LM**. 1990. The effect of chronic phencyclidine (PCP) and phenylcyclohexene (PC) on lymphocyte in subsets in rats. *FASEB J* 1990;4:A337.

29. Zorbas M, Owens SM, **Plunkett LM**, Bui H. [3H]TCP protein binding and pharmacokinetics in Sprague-Dawley rat. *FASEB J* 1989;3:A1036.

30. **Plunkett LM**, Kennedy RH, Seifen E. Effects of chronic stress on myocardial beta-adrenergic receptor binding. *The Pharmacologist* 1988;A1300.

31. Evans, R.E., **Plunkett LM**, Kennedy RH, Seifen E. [3H]Ouabain binding to regions of rat heart as determined by autoradiography. *The Pharmacologist* 1988;A41.

32. Massey BW, **Plunkett LM**, Kennedy RH, Seifen E. Alterations in brain angiotensin II binding in the aged rat. Soc. Neuroscience 1987 Abstracts, p. 722.

33. **Plunkett LM**, Alexander N, Saavedra JM. Altered angiotensin II binding in adrenal gland, pituitary gland and brain of sinoaortic denervated rats. Am. Soc. Hypertension. New York, NY, May 1986.

34. Saavedra JM, **Plunkett LM**, Correa FMA. Increased number of angiotensin II binding sites in the subfornical organ of spontaneously hypertensive rates. Am. Soc. Hypertension, New York, NY, May 1986.

35. **Plunkett LM**, Niwa M, Shigematsu K, Saavedra JM. Increased angiotensin II (ANG) binding in superior cervical ganglia of spontaneously hypertensive rats (SHR). *Fed. Proc* 1985;3: 498.

36. **Plunkett LM**, Saavedra JM. Discrete localization of angiotensin II (ANG) binding sites in rat brainstem by quantitative autoradiography. Neural and Endocrine Peptides and Receptors, Symposium, Washington, D.C., May, 1985.

37. **Plunkett LM**, Israel A, Niwa M, Shigematsu K, Saavedra JM. Alterations in angiotensin II binding in pituitary gland, adrenal gland and superior cervical ganglia of spontaneously hypertensive rats (SHR) as determined by quantitative autoradiography. Neural and Endocrine Peptides and Receptors, Symposium, Washington, DC, May 1985.

38. Shigematsu K, Niwa M, **Plunkett LM**, Saavedra JM. High affinity substance P binding sites in rat sympathetic ganglia. Neural and Endocrine Peptide and Receptors, Symposium '85, Washington, DC, May 1985.

39. McCarty R, **Plunkett LM**, Israel A, Saavedra JM. Quantitation of somatostatin binding sites in rat brain. Neural and Endocrine Peptides and Receptors, Symposium '85, Washington, DC, May, 1985.

40. **Plunkett LM**, Saavedra JM. Increased angiotensin II (ANG) binding in brainstem nuclei of adult spontaneously hypertensive rats (SHR) by quantitative autoradiography. Interamerican Society of Hypertension, Cleveland, OH, May 1985.

41. Saavedra JM, **Plunkett LM**, Niwa M, Israel A, Shigematsu K, R. McCarty, Correa FMA. Autoradiographic-microdensitometric methods for the kinetic analysis of neuropeptide receptors and peptidases in individual brain nuclei. IVth World Congress of Biological Psychiatry, Philadelphia, PA, September, 1985.

42. **Plunkett LM** Saavedra JM. 1985. Altered angiotensin II binding in ganglia and brainstem nuclei of spontaneously hypertensive rats (SHR). Council for High Blood Pressure Research, Cleveland, OH, September 1985.

43. **Plunkett LM**, Correa FMA, Saavedra JM. Quantification of angiotensin-1-converting enzyme kinetics in individual rat pituitary and adrenal glands with 125I-MK351A, a specific enzyme inhibitor. Society for Neuroscience, Dallas, Texas, October 1985.

44. McCarty R**, Plunkett LM**, Shigematsu K, Saavedra JM. Quantitative autoradiographic analysis of somatostatin binding sites in discrete areas of rat brain. Society for Neuroscience, Dallas, Texas, October, 1985.

45. Correa FMA, **Plunkett LM,** Saavedra JM. Quantitative autoradiographic determination of angiotensin-converting enzyme distribution in rat brain with 125I-MK351A, a specific inhibitor. Society for Neuroscience, Dallas, Texas, October 1985.

46. **Plunkett LM,** Saavedra JM. Altered angiotensin II binding kinetics in brainstem, pituitary gland, and adrenal gland in adult SHR. 5th International Symposium on SHR and Related Studies, Tokyo, Japan, October, 1985.

47. **Plunkett LM,** Tackett RL. CSF catecholamine activity decreases during cardiac glycoside-induced arrhythmogenesis. *The Pharmacologist* 1985; 25:745.

48. Tackett RL**, Plunkett LM**. Naloxone inhibits the central hypotensive actions of propranolol. *The Pharmacologist* 1983;25:101.

49. **Plunkett LM,** Vallner JJ, Tackett RL. Prazosin lowers plasma digoxin levels. American Heart Assoc, pp 15, Savannah, GA, 1983.

50. Tackett RL**, Plunkett LM**. 1983. BHT 933 lowers blood pressure and increases cerebrospinal fluid norepinephrine levels. American Heart Assoc, pp 16, Savannah GA, 1983.

51. Bayoumi SM, Gokhale R, **Plunkett L,** Vallner JJ. Pharmacokinetics of clortrimazole in dogs. *Acad. Pharmaceut. Sci* 1983;13(2):204, (Miami meeting).

52. **Plunkett LM,** Tackett RL. Central alpha receptors and their role in digitalis cardiotoxicity. *The Pharmacologist* 1982; 24:489A.

53. **Plunkett LM,** Tackett RL. Central alpha antagonism decreases blood pressure in the dog. Proc. Soc. Exp. Biol. Med. S.E. Sec. 7:12A 1982.

PRESENTATIONS

1. **Plunkett, LM.** Reproductive Toxicology. Invited lecture at NYU, Department of Environmental Medicine. October 28, 2020.

2. **Plunkett, L.M.** Provided public comments at the FDA-sponsored public meeting on "Testing Methods for Asbestos in Talc and Cosmetic Products Containing Talc", February 4, 2020.

3. **Plunkett, L.M.** Pesticide Toxicology. Invited lecture at NYU, Department of Environmental Medicine. December 4, 2019.

4. **Plunkett, L.M.** Practical applications of risk assessment. Lecturer at University of Texas Medical Branch at Galveston, Department of Pharmacology and Toxicology. October 19, 2018.

5. **Plunkett, LM.** Non-obviousness and §103. Lecturer at Rutgers School of Law, Camden Campus. November 6, 2012.

6. **Plunkett, LM.** Regulatory primer for pharmacy students: focus on human therapeutics. Invited speaker for the AAPS Visiting Scientist Program, Texas A&M University, College of Pharmacy, Kingsville, TX, May 1, 2009.

7. **Plunkett, LM.** Strategies for reducing adverse drug reactions: Science versus regulatory considerations. Invited speaker for the AAPS Visiting Scientist Program, Texas A&M University, College of Pharmacy, Kingsville, TX, May 1, 2009.

8. **Plunkett, LM.** Novelty requirement of §102. Lecturer at Drexel University School of Law. September 22 and 24, 2008.

9. **Plunkett, LM.** Novelty requirement of §102. Lecturer at Rutgers School of Law, Camden Campus. September 22 and 24, 2008.

10. **Plunkett, LM.** Discussion of the Adequacy of Current Regulatory Risk Assessment Approaches for Protection of Children's Health and the Health of Other "Sensitive" Human Subpopulations. Testimony before the U.S. Senate Enviornment and Public Works Committee. April, 29, 2008.

11. **Plunkett, LM.** Strategies for reducing adverse drug reactions: Science versus regulatory considerations. Invited speaker for the AAPS Visiting Scientist Program, Florida A&M University, Tallahassee, FL, October 26, 2006.

12. **Plunkett, LM**. The guidance as currently implemented: experience with Minnesota's draft risk levels. Presented at the ISRTP workshop entitled: EPA's New (Proposed) Guidance for Assessing Cancer Risks from Early Life Exposures. Genotoxic Mode of Action and Implications for Human Health-Based Standards. Baltimore, MD February 10, 2005.

13. **Plunkett, LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 17, 2004.

14. **Plunkett, LM**. Moderator of the symposium entitled "Regulation of genetically modified cells, foods, organisms and animals for consumer and therapeutic use. Meeting of the American Association of Pharmaceutical Sciences (AAPS), Baltimore, MD, November 11, 2004.

15. **Plunkett, LM**. A Road map to the US Food And Drug Administration Regulations. Invited Speaker and Session Co-chair, Federation of European Biochemical Societies (FEBS), Istanbul, Turkey, October 20-24, 2002.

16. **Plunkett, LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 2001.

17. **Plunkett, LM** . Differences and Similarities Between Children and Adults in their Exposure and Response to Environmental Chemicals: An Update Since 1992. Invited Speaker at ToxForum, Aspen CO, July 2001.

18. **Plunkett, LM**. Do current FIFRA guideline tests protect infants and children? Lead as a case study. Invited speaker at the Sixteenth International Neurotoxicology Conference, Pesticides and Susceptible Populations: Who is at Risk and When? Little Rock, Arkansas, September 13-16 1998

19. **Plunkett, LM**. An overview of biotechnology regulations: the USFDA and the USEPA. Lecturer at University of Houston at Clearlake, October 16 1998.

20. Rodricks, JV, Santamaria, AB, **Plunkett, LM**. Risk Assessment as a Tool in Litigation: A Discussion of the Uses and Their Limits [Presented by **Plunkett LM**]. Society for Risk Analysis, , New Orleans, LA. December 10 1996.

21. **Plunkett, LM**. Current Issues in Lead Exposure and Risk Assessment. Symposia at the annual meeting of The American College of Toxicology, Valley Forge, PA. November 9 1996.

22. **Plunkett, LM** . An Overview of Biotechnology Regulations: Environmental Regulations. Lecturer at the South Texas School of Law, October 1995.

23. **Plunkett, LM**. An Overview of Biotechnology Regulations: FDA Regulations. Lecturer at the South Texas School of Law, October 1995.

24. **Plunkett, LM** . A Discussion of Toxicokinetics. Featured speaker at a symposium at the Int. Congress of Toxicol., July 5 1995.

25. **Plunkett, LM**. Chutes and Ladders: The Hazardous Journey for R&D to Market. Featured speaker at the Futurist's Conference, Irvine, CA, June 28, 1995.

BOOK CHAPTERS

1. Anderson, SA**, Plunkett,LM.** 2020. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

2. Anderson, SA, **Plunkett, LM.** 2019. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

3. **Plunkett, LM**, O'Donnell, JT. 2016. Ketorolac abuse and injury in college athletics. In: *O'Donnell's Drug Injury, Fourth Edition*. O'donnell and O'Donnell (eds.), Lawyers & Judges Publishing Company, Inc: Tucson, AZ, pp. 591-602.

4. **Plunkett, LM,** Timmerman, LE. 2011. Pharmacovigilance and Postmarket Surveillance in the United States: The Role of the U.S. Food and Drug Administration. In: Elements of Pharmacovigilance: Be Vigilant, Be Safe. R. Sehgal *et al.* (Eds.), Kongposh Publications: New Dehli.

5. Rodricks, JV, Frankos, VH, **Plunkett, LM**. 1995. Food Additives. In: Regulatory Toxicology. C.P. Chengelis, J.F. Holson and S.C. Gad (eds.) Raven Press, New York, New York, 51-82.

6. **Plunkett, LM**, Turnbull, D, Rodricks, JV. 1992. Differences between adults and children affecting exposure assessment. In: Similarities and Differences Between Children and Adults: Implications for Risk Assessment. P.S. Guzelian, C.J. Henry and S.S. Olin (eds.) ILSI Press, Washington D.C., 79-96.

7. Saavedra JM, **Plunkett LM**, Correa FMA, Israel A, Kurihara M, Shigematsu K. 1986. Quantitative autoradiography of angiotensin and atrial natriuretic factor binding sites in brain nuclei of spontaneously hypertensive rats. In Brain Peptides and Catecholamines in Cardiovascular Regulation in Normal and Disease States.

MISCELLANEOUS

1. **Plunkett LM.** 2008. U.S. Senate Committee on Environment & Public Works. Oral testimony. Full Committee hearing entitled "Oversight on EPA Toxic Chemical Policies". Tuesday, April 29, 2008.

2. **Plunkett LM**, Brett SM. 1991. A new look at lead: sources, exposures, and uptake in populations at risk. ENVIRON Report. 5:6-9.

3. **Plunkett LM**, Frankos VH. 1991. FDA re-examines the safety of silicone gel-filled breast implants. ENVIRON Report. 5:10-13.

APPENDIX B

Testimony List

List of Testimony for Dr. Laura M. Plunkett, Ph.D, DABT

Year	Case Name	Law Firm Represented
2018	*Crochet v. BMS and Otsuka Pharmaceutical* *Deposition* *11 January 2018*	Javier Law Firm (New Orleans, LA)
2018	*Mirena MDL* *Deposition* *19 January 2018*	Jones, Ward (Louisville, KY)
2018	*Synthes case* *Deposition* *24 January 2018*	Nations Law Firm (Atlanta, GA)
2018	*Boone v. BIPI* *Trial Testimony* *27-28 February, 01-02 March 2018*	Nemeroff Law Firm (Dallas, TX)
2018	*Gallum v. BIPI* *Trial Testimony* *18-20 April 2018*	Nemeroff Law Firm (Dallas, TX)
2018	*Fluoroquinolones MDL* *Deposition* *25 April 2018*	Baron & Budd, P.C. (Dallas, TX)
2018	*Xarelto MDL* *Cooney case* *Deposition* *24 May 2018*	The Lambert Law Firm (New Orleans, LA)
2018	*Xarelto MDL* *Cooney case* *Trial Testimony* *09 August 2018*	The Lambert Law Firm (New Orleans, LA)

Year	Case Name	Law Firm Represented
2018	*Pradaxa* *Bedsole v. BIPI* *Trial Testimony* *17th, 18th, 20th, 21st September 2018*	Myers & Flowers (St. Charles, IL)
2018	*McCants v. Vitacost, Inc.* *Deposition* *25 September 2018*	Miller Weisbrod (Dallas, TX)
2018	*Talc* *Brower case Georgia* *Deposition* *28 September 2018*	Beasley Allen (Montgomery, AL)
2018	*Pradaxa* *Knight case (West Virginia)* *Trial Testimony* *04 October – 05 October 2018*	Childers, Schlueter & Smith (Atlanta, GA)
2018	*Cell Phone Litigation* *Deposition Testimony* *November 15, 2018*	Lundy, Lundy, Soileau & South (Lake Charles, LA)
2018	*Gadolinium* *Kish v. GE Electric* *Deposition Testimony* *27 November 2018*	Power Rogers & Smith, PC
2018	*Taxotere* *Deposition Testimony* *10 December 2018*	The Lambert Law Firm (New Orleans, LA)
2018	*Talc* *Brower case Georgia* *Deposition* *18 December 2018*	Beasley Allen (Montgomery, AL)
2018	*Talc MDL* *Deposition* *19 December 2018*	Ashcraft & Gerel LLP (Alexandria, VA)

Year	Case Name	Law Firm Represented
2019	*Pradaxa Litigation* *Supplemental Deposition* *07 Janaury 2019*	The Nemeroff Firm (Dallas, TX)
2019	*Kubicki v. Medtronic, Inc. et al* *Deposition* *06 March 2019*	Ashcraft & Gerel LLP (Alexandria, VA)
2019	*McCants v. Vitacost, Inc.* *Trial Testimony* *29 March ; 01 April 2019*	Miller Weisbrod (Dallas, TX)
2019	*Daniels-Feasel et al v. Forest Pharmaceuticals, Inc., et al* *Deposition* *12 April 2019*	Nidel & Nace PLLC (Washington, DC)
2019	*Taxotere* *Deposition* *22 April 2019*	David F. Miceli, LLC (Carrollton, GA)
2019	*Pradaxa Litigation* *Ridings v. BIPI* *27 April 2019*	Humphreys, Farrington & McClain (Independence, MO)
2019	*Roberto v. BIPI* *Trial Testimony* *1-3 May 2019*	Ury, Moskow (Fairfield, CT)
2019	*Emley, Donna v. Wal-Mart Stores, Inc., et al.* *Deposition* *14 May 2019*	Childers, Schlueter & Smith (Atlanta, GA)
2019	*Ruiz v. TEVA, et al* *Deposition* *10 June 2019*	Searcy, Denney, Scarola, Barnhart & Shipley (West Palm Beach, FL)
2019	*Pleasant v. Wellington Regional Med Ctr, et al.* *Deposition* *02 July 2019*	Searcy, Denney, Scarola, Barnhart & Shipley (West Palm Beach, FL)

Year	Case Name	Law Firm Represented
2019	*Thomas, et al. v. Mobil Oil Corp, et al* *Deposition* *10 July 2019*	Fransen & Hardin, PLC (New Orleans, LA)
2019	*Ruiz v. TEVA, et al* *Deposition (continuation of 10 June deposition)* *31 July 2019*	Searcy, Denney, Scarola, Barnhart & Shipley (West Palm Beach, FL)
2019	*Coleman case (Cook Medical)* *Deposition* *01 August 2019*	Matthews & Associates (Houston, TX)
2019	*Talc* *Brower case Georgia (J&J)* *Trial* *12-16 September 2019*	Beasley, Allen (Montgomery, AL)
2019	*Taxotere MDL* *Trial* *18 September 2019*	David F. Miceli, LLC (Carrollton, GA)
2019	*Lilla v. Cordis Corporation* *Deposition* *16 October 2019*	Freese & Goss (Dallas, TX)
2019	*Ridings v. BIPI* *Hearing* *28-29 October 2019*	Humphreys, Farrington & McClain (Independence, MO)
2019	*Lilla v. Cordis Corporation* *Deposition (CONTINUATION)* *31 October 2019*	Freese & Goss (Dallas, TX)
2019	*Seegert, et al. V. Rexall Sundown, Inc.* *Deposition* *06 November 2019*	Blood Hurst & O'Reardon, LLP (San Diego, CA)
2019	*Six v. CSX Corporation* *Deposition* *11 November 2019*	Franklin Law, LLC (Savannah, GA)

Year	Case Name	Law Firm Represented
2019	*Cadigan v. Johnson & Johnson (Talc)* *Deposition* *13 November 2019*	Beasley Allen (Montgomery, AL)
2019	*Crayton & Thibodeaux case (Taxotere)* *Deposition* *19 November 2019*	David F. Miceli, LLC (Carrollton, GA)
2019	*Lyons v. BIPI (Pradaxa)* *Deposition* *25 November 2019*	Ury, Moskow (Fairfield, CT)
2019	*Forrest v. Johnson & Johnson (Talc)* *Trial Testimony* *06, 09-10 December 2019*	Beasley Allen (Montgomery, AL)
2019	*Crayton & Thibodeaux case (Taxotere)* *Deposition (**CONTINUATION**)* *13 December 2019*	David F. Miceli, LLC (Carrollton, GA)
2020	*McDermitt case* *Deposition* *21 January 2020*	Goldenberg Law, PLLC (Minneapolis, MN)
2020	*Benitez v. Dr. Ronald Seguar* *Deposition* *23 January 2020*	Orrill & Malbrough, LLC (Metairie, LA)
2020	*State of Hawai'i (Clare E. Connors, Attorney General) v. Bristol-Myers Squibb (BMS) et al.* *Deposition* *21 February 2020*	Baron and Budd (Encino, CA)
2020	*Kahn case (Taxotere)* *Deposition* *27 April 2020*	David F. Miceli, LLC (Carrollton, GA)
2020	*Sandra Sutter v. Cordis (IVC)* *Deposition* *27 May 2020 and 8 June 2020*	Blankenship Law Firm (Dallas, TX)

Year	Case Name	Law Firm Represented
2020	*Roney v. Provient* *Deposition* *20 July 2020*	Smith, LaCien LLP (Chicago, IL)
2020	*Taxotere 505b2 Cases* *03 & 08 September 2020*	David F. Miceli, LLC (Carrollton, GA)
2020	*State of Hawai'i (Clare E. Connors, Attorney General) v. Bristol-Myers Squibb (BMS) et al.* *Trial* *26-27 October 2020*	Baron and Budd (Encino, CA)
2021	*Kahn case (Taxotere)* *Deposition* *7 April 2021*	David F. Miceli, LLC (Carrollton, GA)
2021	*Cadigan v. Johnson & Johnson (Talc)* *Trial Testimony* *14-16 July 2021*	Beasley Allen (Montgomery, AL)
2021	*Talc MDL* *Deposition* *10 August 2021*	Ashcraft & Gerel LLP (Alexandria, VA) Beasley Allen (Montgomery, AL)
2021	*Kleiner v. Johnson & Johnson (Talc)* *Trial Testimony* *18-20 and 23-24 August 2021*	Beasley Allen (Montgomery, AL)
2021	*Geise et al. v. Johnson & Johnson (Talc)* *Trial Testimony* *10, 13-14 September 2021*	Beasley Allen (Montgomery, AL)
2021	*Guilbault and Plaisance v. 505b2 Defendants* *Deposition* *24 September 2021*	David F. Miceli, LLC (Carrollton, GA)
2021	*Kahn v. Sanofi Aventis* *Trial Testimony* *12 November 2021*	David F. Miceli, LLC (Carrollton, GA)

Year	Case Name	Law Firm Represented
2021	*State of New Mexico v. Bristol-Myers Squibb (BMS) et al.* *Deposition* *19 November 2021*	Baron & Budd (Encino, CA)
2021	*Mooneyham v. Bactolac* *9 December 2021*	Beasley Allen (Montgomery, AL)
2022	*Earnest case (Taxotere)* *Deposition* *01 June 2022*	David F. Miceli, LLC (Carrollton, GA)

APPENDIX C

Reliance List

Deposition of Antony Raj Gomas 4/9/2021
Deposition of Daniel Snider 3/31/2021 & 4/23/2021
Deposition of Eric Gu 4/5-6/2021
Deposition of Hai Wang 3/10-11/2021
Deposition of Jucai Ge 4/27/2021
Deposition of Jucai Ge 4/28/2021
Deposition of Jucai Ge 4/29/2021
Deposition of Jucai Ge 4/30/2021
Deposition of Jucai Ge 5/26/2022
Deposition of Jucai Ge 5/27/2022
Deposition of Jun Du 5/27-28/2021
Deposition of Lin Pan 5/26/2021
Deposition of Min Li 4/20-21/2021
Deposition of Peng Dong 3/29-4/2/2021
Deposition of Remonda Gergis 2/2/2021
Deposition of Richard Glover 3/9/2021, 3/12/2021, 5/25/2021
Deposition of Sushil Jaiswal 6/4/2021
Deposition of Qianming Li 4/13-16/2021
Expert Report of John Quick
Expert Report of Stephen Hecht
FDA Compliance Program Guidance Manual 7356.002F - 9.11.2015
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APL-MDL-2875-0964965
APL-MDL 2875-2983378
APL-MDL-2875-2707753
HUAHAI-US00007899
HUAHAI-US00007752
HLL01193744
MYLAN-MDL2875-00257214
MYLAN-MDL2875-00391203
MYLAN-MDL2875-00708138
PL-Glover008 (MYLAN-MDL2875-00257214)

PL-Glover009
PL-Glover56 (MYLAN-MDL2875-00708138)
PL-Glover57
PRINSTON00183155
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PRINSTON00368120
PRINSTON00463786
PRINSTON00171741
PRINSTON00075797
PRINSTON00463676
SOLCO00025619
SOLCO00025625
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summ-cmc-changes
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TEVA ANDA 077530-002 (eCTD)
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TEVA ANDA 091235-001 (eCTD)
TEVA ANDA 091235-002 (eCTD)
TEVA ANDA 091519-001 (eCTD)
TEVA ANDA 091519-002 (eCTD)
TEVA ANDA 091519-003 (eCTD)
TEVA ANDA 200435-001 (eCTD)
TEVA-MDL2875-00049024
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TEVA-MDL2875-00320639
TEVA-MDL2875-00399168
TEVA-MDL2875-00549883
TEVA-MDL2875-00002463
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TEVA-MDL2875-00020279
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TEVA-MDL2875-00020214

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TEVA-MDL2875-00020212	ZHP00061068
TEVA-MDL2875-00001789	ZHP00061080
TEVA-MDL2875-00154437	ZHP00079913
TEVA-MDL2875-00279311	ZHP00090262
TEVA-MDL2875-00324735	ZHP01681999
TEVA-MDL2875-00614800	ZHP00090441
TEVA-MDL2875-00733964	ZHP00092392
TORRENT-MDL2875-00232735	ZHP00101881
TORRENT-MDL2875-00116577	ZHP00101882
TORRENT-MDL2875-00291332	ZHP00101913
TORRENT-MDL2875-00539890	ZHP00190573
TORRENT-MDL2875-00261545	ZHP00190573 (translated)
TORRENT-MDL2875-00507999	ZHP01303141
TORRENT-MDL2875-00375641	ZHP02614594
TORRENT-MDL2875-00129405	ZHP01916408
TORRENT-MDL2875-00122503	ZHP01427917
TORRENT-MDL2875-00120041	ZHP01460832
TORRENT-MDL2875-00020285	ZHP01748896
TORRENT-MDL2875-00000003	ZHP01812101
TORRENT-MDL2875-00000003	ZHP01812101 (translated)
TORRENT-MDL2875-00000149	ZHP01843066
TORRENT-MDL2875-00000450	ZHP02118072
TORRENT-MDL2875-00000450	ZHP02118712
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TORRENT-MDL2875-00001599	ZHP02630924
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TORRENT-MDL2875-00003084	ZHP00100179
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TORRENT-MDL2875-00003958	ZHP01451842
TORRENT-MDL2875-00005036	ZHP01495188
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Peng Dong Exhibit ZHP 197 – N,N-Dimethylformamide: much more than a solvent. Muzart 2009
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ICH Q3A impurities document
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